



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. FDA-2011-N-0830]

RIN 0910-AF97

Abbreviated New Drug Applications and 505(b)(2) Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), which amended provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) that govern the approval of 505(b)(2) applications and abbreviated new drug applications (ANDAs). This proposed rule would implement portions of Title XI of the MMA that pertain to provision of notice to each patent owner and the new drug application (NDA) holder of certain patent certifications made by applicants submitting 505(b)(2) applications or ANDAs; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This proposed rule also would amend certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER] (see the "Paperwork Reduction Act of 1995" section of this document). See section VII of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the "Paperwork Reduction Act of 1995" section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following way:

- Mail/Hand delivery/Courier (For paper, disk, or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include Docket No. FDA-2011-N-0830 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional

information on submitting comments, see the “Comments” heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Janice L. Weiner, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6268, Silver Spring, MD 20993-0002, 301-796-3601.

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Executive Summary

Purpose of the Regulatory Action

This proposed rule would implement portions of Title XI of the MMA and revise and clarify FDA regulations relating to 505(b)(2) applications and ANDAs in a manner intended to reduce unnecessary litigation, reduce delays in the approval of 505(b)(2) applications and ANDAs that are otherwise ready to be approved, and provide business certainty to both brand name and generic drug manufacturers. The MMA and sections 505, 505A, and 527 of the FD&C Act (21 U.S.C. 355, 355a, and 360cc), in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as our principal legal authority for this proposal.

Title XI of the MMA addressed two key concerns identified in a Federal Trade Commission (FTC) report on anticompetitive strategies that may delay access to generic drugs by: (1) Limiting the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved and (2) establishing conditions under which a first applicant would forfeit the 180-day exclusivity period such that approval of subsequent ANDAs would no longer be blocked. FDA has been implementing the MMA directly from the statute for several years. Based on this experience, FDA is proposing to amend its regulations to implement portions of the MMA that pertain to 30-month stays and other matters not related to 180-day exclusivity.

FDA is proposing to amend its regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act, and to clarify and update these regulations based on recent court decisions and our practical experience implementing provisions related to the approval of 505(b)(2) applications and ANDAs. For

example, we are proposing to clarify requirements for the NDA holder's description of the patented method of use (the "use code") required for publication in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (commonly known as the Orange Book) to avoid overbroad use codes that may delay approval of generic drugs. This is intended to facilitate FDA's implementation of the statutory provisions that permit 505(b)(2) and ANDA applicants to omit ("carve out") protected conditions of use from labeling and obtain approval for conditions of use that are not covered by unexpired patents or exclusivity. As the U.S. Supreme Court recently noted in Caraco Pharm. Labs. v. Novo Nordisk A/S: "An overbroad use code... throws a wrench into the FDA's ability to approve generic drugs as the statute contemplates" (132 S. Ct. 1670, at 1684 (2012)).

Finally, we are proposing to update the regulations to codify FDA's current practice and policy and thereby promote transparency.

Summary of the Major Provisions of the Regulatory Action

Submission of Patent Information. The proposed rule would revise and streamline requirements related to submission of patent information on: (1) Patents that claim the drug substance and/or drug product and meet the requirements for patent listing on that basis; (2) drug substance patents that claim only a polymorph of the active ingredient; and (3) certain NDA supplements. The proposed rule would clarify requirements for the submission of information related to patents that have been reissued by the Patent and Trademark Office (PTO). The proposed rule describes our approach to treating the original and reissued patents as a "single bundle" of patent rights, which first became relevant to approval of 505(b)(2) applications and ANDAs with the submission of the original patent information.

We are proposing to codify our long-standing requirement that the NDA holder's description of the patented method of use required for publication in the Orange Book must contain adequate information to assist FDA and 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. To restrain overbroad use codes, the proposed rule would expressly require that if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder's use code must describe only the specific portion(s) of the indication or other method of use claimed by the patent.

Timing of Submission of Patent Information. We are proposing to expressly describe our current practice with respect to listing patent information that has not been submitted to FDA within 30 days after patent issuance. Although we list untimely filed patents pursuant to section 505(c)(2) of the FD&C Act, we generally do not require an applicant with a pending 505(b)(2) application or ANDA to provide a patent certification to the untimely filed patent. Thus, the untimely filed patent will neither delay approval of a pending 505(b)(2) application or ANDA until patent expiration nor necessitate a carve-out of information related to a patented method of use.

We are proposing to expand the category of untimely filed patent information to include certain amendments to the NDA holder's description of the approved method(s) of use claimed by the patent, if such changes do not relate to a corresponding change in approved labeling or are submitted more than 30 days after such labeling change. This proposed regulatory revision is intended to reduce delays in approval related to manipulation of patent use codes in a manner not contemplated by the FD&C Act.

In addition, we are proposing to establish that the submission date of patent information provided by an NDA holder after approval would be the earlier of the date on which Form FDA 3542 is date-stamped by the Office of Generic Drugs (OGD) Document Room or officially received electronically by FDA. These proposed revisions are intended to facilitate prompt listing in the Orange Book and to remove any ambiguity about the date of submission in light of the implications for the patent certification obligations of 505(b)(2) and ANDA applicants that rely upon the listed drug.

Correction or Change of Patent Information. We are proposing to enhance FDA's response to challenges to the accuracy or relevance of submissions of patent use code information to the Agency, in certain circumstances. If, in response to such a challenge, the NDA holder confirms the accuracy of the information, fails to timely respond, or submits a revision to the use code that does not provide adequate clarity for FDA to determine whether the scope of a proposed labeling carve-out would be appropriate based on the NDA holder's use code and approved labeling, we are proposing to review proposed labeling carve-out(s) for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent. In addition, we are proposing to expressly require the correction or change of patent information by the NDA holder if: (1) The patent or patent claim no longer meets the statutory requirements for listing; (2) the NDA holder is required by court order to amend patent information or withdraw a patent from the list; or (3) the term of a listed patent is extended under patent term restoration provisions. These proposed revisions would facilitate implementation of the MMA provision related to patent withdrawal and efficient enforcement of the FD&C Act.

Notice of Paragraph IV Certification--Timing. We are proposing to revise our regulations to clearly delineate the two limitations on the time frame within which notice of a paragraph IV certification can be provided to the NDA holder and each patent owner: (1) The date before which notice may not be given (reflecting FDA's long-standing practice) and (2) the date, established by MMA, by which notice must be given.

For an original application, a 505(b)(2) or ANDA applicant must send notice of a paragraph IV certification on or after the date on which it receives an "acknowledgment letter" or a "paragraph IV acknowledgment letter" from FDA stating that the application is sufficiently complete to permit a substantive review, but not later than 20 days after the date of the "postmark" (as defined in the proposed rule) on such letter.

For an amendment or supplement, a 505(b)(2) or ANDA applicant must send notice of a paragraph IV certification contained in an amendment to an application (that has been received for substantive review) or in a supplement to an approved application at the same time that the amendment or supplement is submitted to FDA. We are proposing to establish a date (the first working day after the day the patent is published in the Orange Book) before which an ANDA applicant cannot send valid notice of a paragraph IV certification to a newly listed patent. This approach is intended to promote equity among ANDA applicants seeking eligibility for 180-day exclusivity and to reduce the burden on industry and FDA associated with serial submissions and multiple notices of paragraph IV certifications related to a newly issued patent.

Notice of a paragraph IV certification that has been sent prematurely is invalid, and will not be considered to comply with the FD&C Act's notice requirement. We are proposing administrative consequences for ANDA applicants who fail to send notice of paragraph IV certification within the statutory time frame established by the MMA. The date the ANDA was

submitted would be deemed to be delayed by the number of days by which the time frame was exceeded, which may result in the applicant losing eligibility for 180-day exclusivity.

Notice of Paragraph IV Certification--Content and Methods. We are proposing revisions to the content of notice of a paragraph IV certification to incorporate requirements added by the MMA and to support the efficient enforcement of our regulations. We also are proposing to expand the acceptable methods of sending notice of a paragraph IV certification beyond registered or certified mail to include “designated delivery services.” This would reduce the burden on 505(b)(2) and ANDA applicants who currently must submit requests to send notice by common alternate delivery methods.

Amended Patent Certifications. We are proposing to clarify the requirements for a 505(b)(2) or ANDA applicant to amend a paragraph IV certification after a judicial finding of patent infringement to reflect statutory changes made by the MMA. We also are proposing to clarify the circumstances and time frame in which a 505(b)(2) or ANDA applicant must submit an amended patent certification after an NDA holder has withdrawn a patent and requested removal of the patent from the Orange Book. The proposed rule would codify our current practice of not removing a withdrawn patent from the list until FDA has determined that no first applicant is eligible for 180-day exclusivity or such exclusivity is extinguished, and exempting 505(b)(2) applicants from providing or maintaining a certification to withdrawn patents. The proposed rule also clarifies an applicant’s current patent certification obligations with respect to a reissued patent, and proposes implications for 180-day exclusivity and a 30-month stay. In addition, the proposed rule would expressly codify the current requirement for a 505(b)(2) or ANDA applicant to submit a patent certification to a newly issued patent that claims the listed drug or an approved method of use.

Amendments or Supplements: Patent Certification Requirements. We are proposing to clarify and augment the patent certification requirements for amendments and supplements to 505(b)(2) applications and ANDAs to ensure that changes to the drug product that could be protected by patent are accompanied by a new patent certification. A new patent certification currently is required to accompany an amendment or supplement to add a new indication or other condition of use, or to add a new strength or change an existing strength. The regulations also currently require a patent certification to be amended if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate. We are proposing to augment this regulation by requiring a new patent certification with an amendment to make other-than-minor changes in product formulation or to change the physical form or crystalline structure of the active ingredient.

Limitation on Submission of Certain Amendments and Supplements to a 505(b)(2) Application or ANDA. We are proposing to codify our current interpretation of the MMA's prohibition on submitting an amendment or a supplement to seek approval of: (1) "[A] drug that is a different drug" than the drug identified in the original 505(b)(2) application; or (2) "a drug referring to a different listed drug" than the drug cited as the basis for ANDA submission. We are implementing these parallel restrictions on submission of certain types of changes in an amendment or a supplement to a 505(b)(2) application or ANDA in a manner that is consistent with the statutory text and preserves a meaningful opportunity for a single 30-month stay.

505(b)(2) Applications. We are proposing to require a 505(b)(2) applicant to identify a pharmaceutically equivalent product, if already approved, as a listed drug relied upon, and comply with applicable regulatory requirements. This is intended to help ensure that the

505(b)(2) pathway is not used to circumvent the statutory patent certification obligations that would have applied if the proposed product was not ineligible for approval in an ANDA.

Date of Approval of a 505(b)(2) Application or ANDA. The proposed rule would describe, in a more comprehensive manner, the timing of approval of a 505(b)(2) application or ANDA based on the patent certification(s) or statement(s) submitted by the 505(b)(2) or ANDA applicant. We are proposing to revise the regulations to reflect the MMA's limitation on multiple 30-month stays of approval of a 505(b)(2) application or an ANDA containing a paragraph IV certification to certain patents submitted to FDA on or after August 18, 2003.

We are proposing to clarify that the statutory 30-month stay begins on the later of the date of receipt of notice of paragraph IV certification by any owner of the listed patent or by the NDA holder who is an exclusive licensee (or their representatives). This proposed revision codifies our current practice and provides an efficient means of ensuring that each patent owner or NDA holder receives the full statutory 30-month stay.

We are proposing to codify the MMA's amendments that clarify the type of Federal district and appellate court decisions in patent litigation that will terminate a 30-month stay and lead to approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval. We also are proposing to address other scenarios in which a stay may be terminated, including written consent to approval by the patent owner or exclusive patent licensee, a court order terminating the stay, or a court order of dismissal without a finding of infringement. This is intended to avoid unnecessary delays in approval of generic drugs while upholding the statutory purpose of the stay (i.e., to allow time for patent infringement claims to be litigated prior to approval of the potentially infringing product).

Notification of Commercial Marketing. We are proposing to update the regulations to reflect the MMA provisions that modify the types of events that can trigger the start of the 180-day exclusivity period. A first applicant would be required to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product. If the first applicant does not notify FDA within this time frame, we are proposing to deem the date of first commercial marketing to be the date of the drug product's approval. This may have the effect of shortening the 180-day exclusivity period in a similar manner to the current regulatory consequence for failure to provide "prompt" notice of first commercial marketing.

Notification of Court Actions or Documented Agreements. We are proposing to expand the scope of documentation that an applicant must submit to FDA regarding patent-related court actions and documented agreements to ensure that FDA is promptly advised of information that may affect the timing of approval of a 505(b)(2) application or ANDA.

Costs and Benefits

FDA is proposing to amend the regulations for further implementation of and consistency with the MMA and to make other changes related to 505(b)(2) applications and ANDAs. These changes would improve transparency, facilitate compliance and enforcement, and preserve the balance struck in the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417).

Although many provisions of this proposed rule would codify current practice, elements of this proposal would lead to changes that generate additional benefits and costs. The estimated annual monetized benefits of this proposed rule are \$194,314, and estimated annual monetized costs are \$91,371. We have identified, but are unable to quantify, impacts from proposed

changes to submitted patent information and the implementation of an administrative consequence for ANDA applicants who fail to provide notice of a paragraph IV certification within the time frame required by the MMA.

I. Background

On December 8, 2003, the MMA (Public Law 108-173) was signed into law. Title XI of the MMA significantly amended provisions of the FD&C Act that govern the approval of NDAs described by section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) (505(b)(2) applications) and ANDAs described by section 505(j) of the FD&C Act.

I.A. Hatch-Waxman Amendments

The 505(b)(2) application and ANDA approval pathways were enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions (see H. Rept. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S. Code Congressional and Administrative News 2647 at 2647-2648). With passage of the Hatch-Waxman Amendments, the FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: An NDA, for which the requirements are set out in section 505(b) and (c) of the FD&C Act, and an ANDA, for which the requirements are set out in section 505(j). These categories can be further subdivided into a "stand-alone" NDA, a 505(b)(2) application, an ANDA, and a petitioned ANDA.

A “stand-alone NDA” is an application submitted under section 505(b)(1) of the FD&C Act that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use.

A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature or the Agency’s finding of safety and/or effectiveness for one or more listed drugs).

An ANDA is an application for a duplicate of a previously approved drug that is submitted under the abbreviated approval pathway described in section 505(j) of the FD&C Act. An ANDA must contain information to show that the proposed product is the same as a previously approved drug (the reference listed drug or RLD) with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the drug product selected by the Agency as the reference standard for assessing bioequivalence with the RLD (see section II.A.2.z). (We note that the drug product designated as the RLD may not necessarily be the drug product identified in the Orange Book as the reference standard for bioequivalence studies, for example, for drug product lines with multiple strengths.) An applicant that can meet the requirements for approval under section 505(j) of the FD&C Act may rely upon the Agency’s finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a “stand-alone” NDA submitted under section 505(b)(1) of the FD&C Act.

A “petitioned ANDA” is a type of ANDA for a drug that differs from a previously approved drug product in dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient), for which FDA has determined, in response to a suitability petition submitted under section 505(j)(2)(C) of the FD&C Act, that clinical studies are not necessary to demonstrate safety and effectiveness.

The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA) is subject to the patent and marketing exclusivity protections accorded the listed drug(s) relied upon and the RLD, respectively. An NDA applicant (including a 505(b)(2) applicant) is required to “file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture[,] use, or sale of the drug” (section 505(b)(1) of the FD&C Act). Upon approval of an application under section 505(c) of the FD&C Act, we publish the patent information provided by the applicant in the Orange Book, available electronically on FDA’s Web site at <http://www.fda.gov/cder>.

I.B. Requirements for Patent Certification or Statement

A 505(b)(2) application and ANDA must include a patent certification described in section 505(b)(2) or 505(j)(2)(A)(vii) of the FD&C Act, respectively, for each timely filed patent that claims the listed drug(s) relied upon or RLD, respectively, or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b) or 505(c) of the FD&C Act. For each unexpired patent listed in the Orange Book, the 505(b)(2) or ANDA applicant must submit either a paragraph III certification (section 505(b)(2)(A)(iii) or 505(j)(2)(A)(vii)(III) of the FD&C Act) (delaying approval until the date on

which such patent will expire), a paragraph IV certification (section 505(b)(2)(A)(iv) or 505(j)(2)(A)(vii)(IV) of the FD&C Act) (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application or ANDA is submitted), or, with respect to a method-of-use patent, a statement that the patent does not claim a use for which the applicant is seeking approval (section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act). If the patent information has not been filed with FDA (i.e., is not listed in the Orange Book because the patent information has not been submitted or is not eligible for listing) or the patent has expired, a 505(b)(2) or ANDA applicant may submit a paragraph I certification or paragraph II certification, respectively (see section 505(b)(2)(A)(i) and (ii) and 505(j)(2)(A)(vii)(I) and (II) of the FD&C Act). If, in the opinion of the 505(b)(2) or ANDA applicant and to the best of their knowledge, there are no patents that claim the listed drug(s) relied upon or the RLD, respectively, or that claim a use of such drug, the 505(b)(2) or ANDA applicant may submit a “no relevant patents” certification (see § 314.50(i)(1)(ii) or § 314.94(a)(12)(ii) (21 CFR 314.50(i)(1)(ii) or 314.94(a)(12)(ii)).

An applicant submitting a paragraph IV certification is required to give notice of its paragraph IV certification to the holder of the NDA for the listed drug(s) relied upon or RLD and each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification subjects the 505(b)(2) or ANDA applicant to the risk that it will be sued for patent infringement. If the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there generally will be a statutory 30-month stay of approval of the 505(b)(2) application or ANDA while the patent infringement litigation is pending (see section 505(c)(3)(C) and (j)(5)(B)(ii) of the FD&C Act). ANDA applicants have a statutory incentive to challenge listed patents that may be invalid,

unenforceable, or not infringed by the drug product described in the ANDA. The first applicant to submit a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification may be eligible for a 180-day period of marketing exclusivity (180-day exclusivity) during which approval of subsequent ANDAs containing a paragraph IV certification to a listed patent for the same drug product will not be granted (see section 505(j)(5)(B)(iv) of the FD&C Act).

I.C. Patent Listing Requirements

In July 2002, the FTC published a report on “Generic Drug Entry Prior to Patent Expiration: An FTC Study” (FTC Report) that, among other things, identified circumstances in which ANDA applicants were delayed in entering the market (see http://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy_0.pdf). These circumstances included multiple 30-month stays of approval (related to paragraph IV certifications for additional patents listed after ANDA submission) and a delay in “triggering” the start of a first applicant’s 180-day period of marketing exclusivity thereby blocking subsequent ANDA applicants. In response to the FTC Report, FDA published a proposed rule in October 2002 to amend its patent listing requirements and to permit only a single 30-month stay of approval for a 505(b)(2) application or ANDA (see 67 FR 65448, October 24, 2002) (October 2002 proposed rule). The final rule on “Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of [ANDAs] Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed” was published in June 2003 (68 FR 36676, June 18, 2003) (June 2003 final rule).

I.D. MMA

The MMA was enacted on December 8, 2003, and superseded certain sections of the June 2003 final rule regarding the application of 30-month stays of approval of certain 505(b)(2) applications and ANDAs; the superseded regulations were subsequently revoked by technical amendment (see “Application of 30-Month Stays on Approval of [ANDAs] and Certain [NDAs] Containing a Certification That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed; Technical Amendment” (69 FR 11309, March 10, 2004).

Title XI of the MMA addressed two key concerns identified in the FTC Report by limiting the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved (30-month stays) and by establishing conditions under which a first applicant would forfeit the 180-day exclusivity period such that approval of subsequent ANDAs would no longer be blocked. Section 1101 of the MMA provides that a 30-month stay of approval of a 505(b)(2) application or ANDA is available only if patent infringement litigation was initiated within the 45-day period after receipt of notice of a paragraph IV certification for a patent that had been submitted to FDA before the date of submission of the 505(b)(2) application or ANDA (excluding an amendment or supplement to the application). The resulting incentive for an applicant to change the listed drug relied upon through an amendment of or a supplement to a 505(b)(2) application or ANDA is addressed by the MMA’s prohibition of the submission of certain types of changes (including those requiring reference to a different listed drug) in an amendment of or supplement to a 505(b)(2) application or ANDA. In addition, section 1101 of the MMA amended the FD&C Act to specify the types of court actions that will terminate a 30-month stay of approval.

Section 1101 of the MMA also created new requirements for 505(b)(2) and ANDA applicants sending notice of a paragraph IV certification, including changes to the timing and contents of such notice. In addition, the MMA established conditions under which a 505(b)(2) or ANDA applicant may bring a declaratory judgment action to obtain “patent certainty” (i.e., obtain a judicial determination of non-infringement, invalidity, or unenforceability) with respect to a listed patent for which it has given notice of a paragraph IV certification but has not been sued by the NDA holder or patent owner(s) within the statutory timeframe. If a patent infringement action is initiated against the 505(b)(2) or ANDA applicant, the MMA provides that the applicant may assert a counterclaim seeking an order requiring a correction or deletion of the patent information submitted to FDA for listing by the NDA holder or patent owner.

Section 1102 of the MMA altered the conditions under which a 180-day period of marketing exclusivity is granted by requiring, among other things, that a first applicant lawfully maintain the paragraph IV certification contained in its submission of a substantially complete ANDA. In addition, section 1102 of the MMA established conditions under which a first applicant would forfeit the 180-day exclusivity period.

Section 1103 of the MMA clarified the types of bioavailability and bioequivalence data that can be used to support a 505(b)(2) application or ANDA for a drug that is not intended to be absorbed into the bloodstream.

On March 3, 2004, we published a notice in the Federal Register entitled “Generic Drug Issues; Request for Comments” (69 FR 9982) (Request for MMA Comments) which invited public comment to further identify issues related to the MMA provisions regarding 30-month stays, 180-day exclusivity, and bioavailability and bioequivalence, along with any suggestions

for how to resolve those issues. Comments received in response to the Agency's Request for MMA Comments are addressed in this document, as appropriate.

We are currently implementing the 180-day exclusivity provisions of the MMA directly from the statute and will determine if additional rulemaking is necessary in the future. Where a novel issue of interpretation is raised by a particular factual scenario regarding forfeiture of 180-day exclusivity, we may open a public docket or otherwise seek comment from affected parties in advance of taking action (see, e.g., Docket Nos. FDA-2007-N-0445 (acarbose tablets), FDA-2007-N-0269 (granisetron hydrochloride injection), FDA-2007-N-0035 (ramipril capsules), and FDA-2008-N-0483 (dorzolamide hydrochloride--timolol maleate ophthalmic solution), available at <http://www.regulations.gov>).

We invite interested parties to comment on any aspect of this proposed rule. In addition to requesting general comments on this proposal, we have identified issues throughout this document on which we are specifically seeking comments.

II. Description of the Proposed Rule

This proposed rule implements portions of the MMA that pertain to 30-month stays and other matters not related to 180-day exclusivity, and makes our regulations governing 505(b)(2) applications and ANDAs consistent with amendments made to the FD&C Act by the MMA. In addition, FDA is proposing to amend its regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act, and to clarify and update these regulations based on our practical experience implementing the provisions related to approval of 505(b)(2) applications and ANDAs.

Table 1 summarizes the proposed changes related to FDA's patent listing, patent certification, and 30-month stay regulations in part 314 (21 CFR part 314) and bioavailability and bioequivalence regulations in part 320 (21 CFR part 320):

Table 1.--Highlights of Proposed Changes to FDA's Patent Listing, Patent Certification, and 30-Month Stay Regulations¹

21 CFR Section to Which Changes Apply	Proposed Changes See section of this document (identified in parentheses) for more detailed information regarding the proposed change.
314.3	Overview of New, Revised, and Relocated Definitions (II.A.1) Proposed Amendments to Definitions in § 314.3 (II.A.2) Definitions in Current § 314.108 (II.A.3) Definitions in Current § 320.1 (II.A.4)
314.50(i)(1)	Patent Certification Requirements for Method-of-Use Patents (II.C.1) Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug (II.H)
314.50(i)(2)	Patent Certification Requirements for Method-of-Manufacturing Patents (II.C.2)
314.50(i)(3)	Licensing Agreements (II.C.3)
314.50(i)(4)	Untimely Filing of Patent Information (II.B.2)
314.50(i)(6)	Amended Patent Certifications, including: a. Amended patent certifications after a finding of infringement; b. Amended certifications after a request by the NDA holder to remove a patent from the list; c. Amended certifications upon patent reissuance; and d. Other amended certifications (II.E.1 through II.E.4)
314.52(b) and (d)	Timing of Notice of Paragraph IV Certification, including: a. Date before which notice may not be given; b. Date by which notice must be given; and c. Certification of provision of notice (II.D.1)
314.52(c)	Contents of Notice of Paragraph IV Certification, including: a. Statement that any required bioavailability or bioequivalence studies for a 505(b)(2) application have been submitted; b. Statement confirming receipt of an acknowledgment letter or a paragraph IV acknowledgment letter; c. Documentation that paragraph IV certification was submitted and notice was sent only for patents listed in the Orange Book; and d. Offer of confidential access accompanying notice (II.D.3)
314.52(d)	Notice Required for All Paragraph IV Certifications (II.D.2)
314.52(e)	Documentation of Timely Sending and Receipt of Notice of Paragraph IV Certification, including: a. Acceptable methods of sending notice of paragraph IV certification; and b. Amendment documenting timely sending and confirmation of receipt of notice of paragraph IV certification (II.D.4)

Table 1.--Highlights of Proposed Changes to FDA's Patent Listing, Patent Certification, and 30-Month Stay Regulations¹

21 CFR Section to Which Changes Apply	Proposed Changes See section of this document (identified in parentheses) for more detailed information regarding the proposed change.
314.53(b) and (c)	General Requirements for Submission of Patent Information, including: Revisions to scope of required submission of patent information (II.B.1)
314.53(d)	When and Where To Submit Patent Information, including: a. Submission of patent information for NDA supplements; b. Untimely filing of patent information; c. Where to send submissions of Form FDA 3542a and 3542; and d. Submission date of patent information (II.B.2)
314.53(e)	Public Disclosure of Patent Information (II.B.3)
314.53(f)	Correction or Change of Patent Information, including: a. Patents that claim an approved method of using the drug product (method-of-use patents); and b. Requests by NDA holder to remove patent information from the list (II.B.4)
314.54	Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug (II.H)
314.60(e)	Amendments to an Unapproved 505(b)(2) Application for A Different Drug, including: a. Applications within the scope of section 505(b)(4)(A) of the FD&C Act; b. Proposed amendments subject to section 505(b)(4)(A) of the FD&C Act; c. Exception for amendments to seek approval of a different strength; and (II.G.3)
314.60(f)	Patent Certification Requirements for Amendments to 505(b)(2) Applications (II.F)
314.70(h)	Supplements to a 505(b)(2) Application for A Different Drug (II.G.4)
314.70(i)	Patent Certification Requirements for Supplements to 505(b)(2) Applications (II.F)
314.90	Refusal to Approve an NDA (II.L)
314.93	Petition to Request a Change From a Listed Drug (II.I)
314.94(a)(12)(iii)	Patent Certification Requirements for Method-of-Use Patents (II.C.2)
314.94(a)(12)(iv)	Patent Certification Requirements for Method-of-Manufacturing Patents (II.C.3)
314.94(a)(12)(viii)	Amended Patent Certifications, including: a. Amended patent certifications after a finding of infringement; b. Amended certifications after a request by the NDA holder to remove a patent from the list; c. Amended certifications upon patent reissuance; and d. Other amended certifications (II.E.1 through II.E.4)
314.95(b) and (d)	Timing of Notice of Paragraph IV Certification, including: a. Date before which notice may not be given; b. Date by which notice must be given; and c. Certification of provision of notice (II.D.1)

Table 1.--Highlights of Proposed Changes to FDA's Patent Listing, Patent Certification, and 30-Month Stay Regulations¹

21 CFR Section to Which Changes Apply	Proposed Changes See section of this document (identified in parentheses) for more detailed information regarding the proposed change.
314.95(c)	Contents of Notice of Paragraph IV Certification, including: a. Statement confirming receipt of an acknowledgment letter or a paragraph IV acknowledgment letter; b. Clarification that paragraph IV certifications may be submitted only for patents listed in the Orange Book; and c. Offer of confidential access accompanying notice (II.D.3)
314.95(d)	Notice Required for All Paragraph IV Certifications (II.D.2)
314.95(e)	Documentation of Timely Sending and Receipt of Notice of Paragraph IV Certification, including: a. Acceptable methods of sending notice of paragraph IV certification; and b. Amendment documenting timely sending and confirmation of receipt of notice of paragraph IV certification (II.D.4)
314.96(c)	Amendments to an Unapproved ANDA That Reference a Different Listed Drug, including: a. Approval of a pharmaceutically equivalent RLD in an NDA; b. Changes to the proposed drug product would result in pharmaceutical equivalence to a different RLD; c. Exception for amendments to seek approval of a different strength; and d. Procedure for submission of a new ANDA that identifies a different RLD (II.G.1)
314.96(d)	Patent Certification Requirements for Amendments to ANDAs (II.F)
314.97(b)	Supplements to an ANDA That Reference a Different Listed Drug a. Changes to the proposed drug product would result in pharmaceutical equivalence to a different RLD; b. Exception for supplements to seek approval of a different strength; and c. Procedure for submission of a new ANDA that identifies a different RLD (II.G.2)
314.97(c)	Patent Certification Requirements for Supplements to ANDAs (II.F)
314.99	Refusal to Approve an ANDA (II.L)
314.101	Notification of Filing of a 505(b)(2) Application or Receipt of an ANDA and Other Proposed Revisions (II.J.1 through II.J.2) Administrative Consequence for Late Notice of Paragraph IV Certification (II.D.5)
314.105	Approval of an NDA and ANDA (II.K)
314.107(a)	Date of Approval of a 505(b)(2) Application or ANDA (II.M.1)
314.107(b)	Effect of Patent(s) on the Listed Drug, including: a. Timing of approval based on patent certification or statement; b. Patent information filed after submission of 505(b)(2) application or ANDA; c. Disposition of patent litigation; and d. Tentative approval (II.M.2)
314.107(c)	Subsequent ANDA Submission (II.M.3)
314.107(d)	Delay of Approval Due to Exclusivity (II.M.4)
314.107(e)	Notification of Court Actions or Documented Agreement (II.M.5)

Table 1.--Highlights of Proposed Changes to FDA's Patent Listing, Patent Certification, and 30-Month Stay Regulations¹

21 CFR Section to Which Changes Apply	Proposed Changes See section of this document (identified in parentheses) for more detailed information regarding the proposed change.
314.107(f)	Computation of the 45-day time clock (II.M.6)
314.107(g)	Conversion of Approval to Tentative Approval (II.M.7)
314.108	Definitions in Current § 314.108 (II.A.3)
314.125	Refusal to Approve an NDA (II.L)
314.127	Refusal to Approve an ANDA (II.L)
320.1	Definitions in Current § 320.1 (II.A.4)
320.23	Assessing Bioavailability and Bioequivalence for Drugs Not Intended To Be Absorbed Into the Bloodstream (II.N)

¹ These highlights reference important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.A. Definitions

II.A.1. Overview of New, Revised, and Relocated Definitions

We are proposing to amend § 314.3(b) to define terms relevant to amendments to the FD&C Act made by the MMA and to add definitions of terms that have been used by the Agency for several years in the context of implementing section 505(b) and (j) of the FD&C Act. We also are proposing amendments to § 314.3(b) and elsewhere to conform with other changes that we are proposing in this regulation and to incorporate new definitions. Although some of these revisions are not required for implementation of the MMA, these proposed changes are intended to enhance the clarity of our regulations in part 314 and promote consistency throughout our regulations.

Several definitions that we are proposing to add to § 314.3(b) involve terms that are defined specifically by the MMA (see definitions of “180-day exclusivity,” “first applicant,” “substantially complete application,” and “tentative approval” in section II.A.2. Our proposed definitions of these terms closely track the statutory language with only minor editorial changes (see section 505(j)(5)(B)(iv)(I) and (j)(5)(B)(iv)(II) of the FD&C Act). We also are proposing to add definitions of a “paragraph IV acknowledgment letter” and an “acknowledgment letter” to

§ 314.3(b), as the term “paragraph IV acknowledgment letter” is relevant to amendments made to section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act regarding timing requirements for notices of paragraph IV certifications (see section II.A.2).

We are proposing to add definitions of terms that have been commonly used by the Agency over the years in the context of implementing section 505(b) and (j) of the FD&C Act and part 314, but that have not been expressly defined in § 314.3(b) (see definitions of “abbreviated new drug application,” “ANDA,” “dosage form,” “new drug application,” “NDA,” “ANDA holder,” “NDA holder,” “patent owner,” “reference standard,” “strength,” and “therapeutic equivalents” in section II.A.2). These proposed definitions are intended to codify our longstanding use of these terms, rather than substantively change the meaning.

We are proposing to revise the definitions of certain existing terms in § 314.3(b) (see definitions of “listed drug” and “the list” in section II.A.2) to conform with other changes we are proposing in this regulation and to clarify the distinction between approvals and tentative approvals (see section II.K). We also are proposing to revise the definitions of “abbreviated application” and “applicant” in § 314.3(b) to reflect statutory changes made by the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (FDAMA) that eliminated the previous need to distinguish between ANDAs and abbreviated antibiotic applications. We are proposing amendments to § 314.3(b) and elsewhere to incorporate terms used by the Agency into existing definitions (see proposed amendments to definition of “applicant” to use terms “NDA” and “ANDA” in lieu of “application” and “abbreviated application,” respectively, in section II.A.2).

For clarity and ease of reference, we are proposing to add definitions of “paragraph IV certification” and “commercial marketing” to § 314.3(b) based on the current use of these terms

in other sections of part 314. As discussed in section II.A.2.v, a paragraph IV certification is defined by section 505(b)(2)(A)(iv) and (j)(2)(A)(vii)(IV) of the FD&C Act and currently described in implementing regulations in part 314. Commercial marketing of certain drug products is a statutory trigger for beginning the period of 180-day exclusivity and is described in current and proposed regulations (see sections II.A.2.1 and II.M.3). We also are proposing to move the definitions of the terms “active moiety” and “date of approval” in current § 314.108(a) to § 314.3(b). These definitions are relevant to matters covered in other sections of part 314 and thus appropriate for inclusion in the general definition section for this part.

We also are proposing to add definitions of “active ingredient,” “inactive ingredient,” and the related term “component” to § 314.3(b) based on the current definitions in § 210.3(b) (21 CFR 210.3(b)). These definitions reflect the current use of these terms in other sections of part 314.

Finally, we are proposing to move the definitions that currently are in § 320.1(a) through (g) to § 314.3(b) for ease of reference and organizational convenience. The terms currently defined in § 320.1 (“bioavailability,” “drug product,” “pharmaceutical equivalents,” “pharmaceutical alternatives,” “bioequivalence,” “bioequivalence requirement,” and “same drug product formulation”) are relevant to matters covered in part 314 in addition to matters in part 320, and certain of these terms are already used in part 314. (As noted elsewhere in this document, our proposed amendments to part 320 (discussed in section II.N) would make clear that proposed terms defined in § 314.3 will be applicable to part 320 when those terms are used in part 320.) With three exceptions (the definitions of “bioavailability,” “bioequivalence,” and “drug product,” discussed in section II.A.2), we are proposing to move the definitions in existing § 320.1(a) through (g) to § 314.3(b) without changes. We are proposing to modify the definition

of bioavailability in current § 320.1(a) to reflect a statutory change made by the MMA. We are proposing conforming revisions to the definition of bioequivalence. It is not necessary to move the definition of drug product in § 320.1(b) to § 314.3 because this section already includes a definition of drug product that we believe is functionally identical.

II.A.2. Proposed Amendments to Definitions in § 314.3

II.A.2.a. 180-day exclusivity period. The MMA defines the term “180-day exclusivity period” for purposes of section 505(j)(5) of the FD&C Act to mean “the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause” (see section 505(j)(5)(B)(iv)(II)(aa) of the FD&C Act). We are proposing to supplement this definition for ANDAs subject to the MMA to incorporate the statutory trigger for 180-day exclusivity, as described in section 505(j)(5)(B)(iv)(I) of the FD&C Act, and make minor editorial changes. In proposed § 314.3(b), the term “180-day exclusivity period” is defined as the 180-day period beginning on the date of the first commercial marketing of the drug (including the commercial marketing of the RLD) by any first applicant of an ANDA (see discussion of “commercial marketing” and “first applicant” in sections II.A.2.l and II.A.2.q). The 180-day period ends on the day before the date on which an ANDA submitted by an applicant other than a first applicant could be approved (see section 505(j)(5)(B)(iv)(I) through (j)(5)(B)(iv)(II)(aa) of the FD&C Act). As reflected in the parenthetical reference to commercial marketing of the RLD, the 180-day exclusivity period may be triggered by the commercial marketing of an “authorized generic drug,” as that term is currently defined in § 314.3(b).

FDA interprets the 180-day exclusivity provisions added by the MMA to apply only to ANDAs referring to an RLD for which the first ANDA was submitted after December 8, 2003,

whether or not that ANDA contained a paragraph IV certification at the time of submission (see section 1102(b)(1) of the MMA (Effective Date provision)). If one or more ANDAs were submitted before December 8, 2003, but the first paragraph IV certification was submitted in an ANDA after that date, all ANDAs would be governed by the pre-MMA 180-day exclusivity provisions in order to impose the same statutory exclusivity scheme on all ANDAs referencing a specific RLD and avoid a possible disparate effect on ANDA applicants simultaneously undertaking the same patent challenge (see FDA's letter to ANDA applicants for topiramate sprinkle capsules dated April 15, 2009, available on FDA's Web site at <http://www.fda.gov>).

II.A.2.b. Abbreviated application, abbreviated new drug application, or ANDA. We are proposing to revise the definition of “abbreviated application” to include the alternate terms “abbreviated new drug application” and “ANDA” for clarity and administrative efficiency. Conforming revisions have been proposed throughout the sections of parts 314 and 320 in this rulemaking to incorporate the commonly used acronym “ANDA” in place of references to “abbreviated application” and “abbreviated new drug application.”

In addition, we are proposing to delete the text in § 314.3(b) that explains that the term “ ‘[a]bbreviated application’ applies to both an abbreviated new drug application and an abbreviated antibiotic application” to reflect statutory changes made by FDAMA. Section 125 of FDAMA repealed section 507 of the FD&C Act under which marketing applications, including ANDAs, for antibiotics had been approved. FDAMA provided that ANDAs for antibiotics previously approved under section 507 of the FD&C Act would be deemed approved under section 505(j) of the FD&C Act. We note that there have been subsequent amendments to the FD&C Act involving applications for antibiotic drugs (see QI Program Supplemental Funding

Act of 2008, Public Law 110-379 (2008)); however, these amendments are not specifically addressed in this proposed rulemaking.

II.A.2.c. Acknowledgment letter. We are proposing to define the term “acknowledgment letter” as a counterpart to the term “paragraph IV acknowledgment letter,” which is proposed for inclusion in § 314.3(b) to facilitate implementation of the MMA’s requirements for the timing of notice of a paragraph IV certification (see sections II.A.2.u and II.D.1). We propose to define “acknowledgment letter” as a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA is sufficiently complete to permit a substantive review. The proposed definition states that an acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received. An acknowledgment letter is used for 505(b)(2) applications and ANDAs that contain a patent certification or statement other than a paragraph IV certification for the listed drug(s) relied upon or RLD, respectively (compare definition of “paragraph IV acknowledgment letter” discussed in section II.A.2.u).

Although the term “acknowledgment letter” applies to both 505(b)(2) applications and ANDAs that contain a patent certification or statement other than a paragraph IV certification, there are important practical differences between the letters for each type of application. In FDA’s Center for Drug Evaluation and Research (CDER), the Office of Generic Drugs (OGD) reviews ANDAs after submission to determine whether the ANDA may be received for substantive review under § 314.101(b)(1). OGD will send an acknowledgment letter (or a paragraph IV acknowledgment letter, if appropriate) to the applicant after a determination has been made that the ANDA is sufficiently complete to permit a substantive review.

For NDAs, including 505(b)(2) applications, a determination regarding whether the application may be filed is made within 60 days after FDA is in receipt of the application as provided in § 314.101(a)(1). In the absence of a refusal to file letter sent to the NDA applicant on or before day 60, the NDA is deemed filed. In the context of a 505(b)(2) application, our proposed definition of “acknowledgment letter” reflects the current practice by CDER’s Office of New Drugs (OND) with respect to its notification of issues identified during the filing review (filing communication) to the applicant generally not later than 14 calendar days after the 60-day filing date. This filing communication is informally known as a “74-day letter” (see Manual of Policies and Procedures (MAPP) 6010.5, “NDAs: Filing Review Issues” (effective May 8, 2003) (available on FDA’s Web site at <http://www.fda.gov>). Under our proposed definition, the filing communication sent by the OND review division to the 505(b)(2) applicant is the "acknowledgment letter" from FDA stating that the 505(b)(2) application is sufficiently complete to permit a substantive review.

It should be noted that if an original ANDA contains a patent certification or statement other than a paragraph IV certification, and the applicant submits an amendment containing a paragraph IV certification before the ANDA has been received for substantive review, the applicant may receive, for administrative reasons, an acknowledgment letter, rather than a paragraph IV acknowledgment letter. This contingency is addressed in proposed § 314.95 by the use of both terms.

II.A.2.d. Act. We are proposing to modify the definition of “act” in § 314.3(b) so that the citation to the U.S. Code reflects sections added to the FD&C Act by FDAMA, the Food and Drug Administration Amendments Act of 2007 (FDAAA), the Food and Drug Administration Safety and Innovation Act (FDASIA), and other legislation.

II.A.2.e. Active ingredient. We are proposing to add the definition of “active ingredient” currently in § 210.3(b)(7) to § 314.3(b) without changes. The term “active ingredient” is relevant to matters covered in part 314 in addition to matters in part 210 and thus appropriate for inclusion in the general definition section for this part.

II.A.2.f. Active moiety. We are proposing to move the definition of the term “active moiety” in current § 314.108(a) to § 314.3(b) without changes. This definition is relevant to matters covered in other sections of part 314 and thus appropriate for inclusion in the general definition section for this part.

II.A.2.g. ANDA holder and NDA holder. We are proposing to define the terms “ANDA holder” and “NDA holder” to mean the applicant that owns an approved ANDA or NDA, respectively. These terms have been commonly used by the Agency over the years in the context of implementing section 505(b) and (j) of the FD&C Act and part 314, but have not been expressly defined in § 314.3(b).

II.A.2.h. Applicant. We are proposing to revise the definition of “applicant” to conform with other changes that we are proposing in this regulation and incorporate the commonly used acronyms “NDA” and “ANDA.” In addition, we are proposing to delete the reference to “an antibiotic drug” in the current definition of “applicant” to reflect statutory changes made by FDAMA that eliminated the previous need to distinguish between a new drug and an antibiotic drug.

II.A.2.i. Application, new drug application, or NDA. We are proposing to revise the definition of “application” to include the alternate terms “new drug application” and “NDA” for clarity and administrative efficiency. Conforming revisions have been proposed throughout the sections of parts 314 and 320 in this rulemaking to incorporate the commonly used acronym

“NDA” in place of references to “application” and “new drug application.” In addition, we are proposing to expressly state that the terms “application, new drug application, or NDA” refer to “stand-alone” applications submitted under section 505(b)(1) of the FD&C Act and to 505(b)(2) applications. Although certain regulations in part 314 refer specifically to 505(b)(2) applications, 505(b)(2) applications also are subject to any applicable regulations governing new drug applications.

We considered replacing the term “application” with “new drug application or NDA,” rather than including “new drug application” or “NDA” as alternate terms, because the term “application” is sometimes used to generally refer to any application (e.g., a “stand-alone” NDA, 505(b)(2) application, or ANDA) in a concise manner. However, such a proposal would have necessitated additional conforming revisions throughout part 314 that are beyond the scope of this rulemaking. We are proposing to replace the term “application” with “NDA or ANDA” in certain sections of part 314 to clarify the text and reflect FDA’s longstanding interpretation of the provision (see, e.g., the definition of “specification” in proposed § 314.3(b)).

II.A.2.j. Bioavailability, bioequivalence. The MMA amended the definitions of “bioavailability” and “bioequivalence” in section 505(j)(8)(A) and (j)(8)(C) of the FD&C Act to confirm that, for drugs not intended to be absorbed into the bloodstream, FDA may “assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action” (emphasis added). For such drugs, the MMA provides that FDA may establish “alternative scientifically valid methods to show bioequivalence ...” (see section 505(j)(8)(C) of the FD&C Act (emphasis added)). Section 1103(b) of the MMA expressly states that the amendments to

section 505(j)(8)(A) and (j)(8)(C) of the FD&C Act “do[] not alter the standards for approval of drugs under section 505(j)” of the FD&C Act.

The amendments to section 505(j)(8)(A) and (C) of the FD&C Act codify FDA’s current practice, based on its existing regulations in §§ 320.1(a) and (e), 320.23(a)(1), and 320.24 and implementation of those regulations, regarding assessment of bioavailability and demonstration of bioequivalence for drugs not intended to be absorbed into the bloodstream (see Schering Corp. v. FDA, 51 F.3d 390 (3d Cir. 1995), cert. denied, 516 U.S. 907 (1995) (holding that FDA’s regulatory standard in § 320.1(e) for bioequivalence of non-systemically effective drugs is a permissible construction of the statute); see also section II.N).

We are proposing to revise the definitions of bioavailability and bioequivalence in § 320.1(a) and (e) to incorporate the textual revisions made in section 505(j)(8)(A) of the FD&C Act and move the revised definitions to § 314.3(b) in light of their relevance to matters covered in part 314 in addition to matters in part 320. The proposed definitions include a statement that for drug products that are not intended to be absorbed into the bloodstream, bioavailability and bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action (emphasis added). FDA will evaluate the scientific appropriateness of methodologies to assess the bioavailability or demonstrate the bioequivalence of non-systemically absorbed drugs based on the best available scientific evidence. We do not interpret section 505(j)(8)(A) and (j)(8)(C) of the FD&C Act to require full analytical method validation (which may have the effect of altering the standards for approval of ANDAs, contrary to section 1103(b) of the MMA), but rather methods that FDA considers to be scientifically valid or appropriate (see Docket No.

FDA-2004-N-0062-0013 (comment submitted by the Biotechnology Industry Organization (BIO)) at 2 to 3, available at <http://www.regulations.gov> (BIO MMA Comment).

To clarify our interpretation of “bioavailability” and conform the definition with terminology used to define bioequivalence, we are proposing to revise the reference to “site of action” in current § 320.1(a) to “site of drug action” (see § 320.1(e)). For locally-acting drug products that are not systemically absorbed or have low systemic bioavailability, a pharmacokinetic comparison of drug and/or metabolite concentrations in plasma would not always reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action (e.g., gastrointestinal tract or lungs). This is consistent with our historical interpretation and application of this term and the express language of section 505(j)(8)(A) of the FD&C Act.

In addition, we are proposing to substitute the term “active moiety” for the statutory term “therapeutic ingredient” in the definitions of “bioavailability” and “bioequivalence.” This approach reflects our longstanding judgment that the term “active moiety” is more appropriate than the term “therapeutic ingredient” in the context of section 505(j)(8)(A) of the FD&C Act (see, e.g., “Abbreviated New Drug Application Regulations”; final rule, 57 FR 17950 at 17972, April 28, 1992) (1992 final rule) (“Congress clearly intended a meaning different from ‘active ingredient’ by the term ‘therapeutic ingredient’ or it would not have used both terms [in what is now section 505(j)(8) of the FD&C Act]. The term ‘active moiety’ refers to the molecule or ion in an active ingredient, excluding those appended portions of the molecule that cause the ingredient to be an ester, or a salt or other noncovalent derivative that is responsible for the physiological or pharmacological action of the ingredient.”)

We also are proposing clarifying revisions in § 314.94(a)(7)(iii) relevant to bioequivalence studies. Proposed § 314.94(a)(7)(iii) would state that the requirements for submission of a description of the analytical and statistical methods used in each bioequivalence study applies to in vitro bioequivalence studies as well as in vivo bioequivalence studies. An in vitro study used to establish or support bioequivalence may include, for example, an in vitro kinetic binding study, an in vitro equilibrium binding study, a permeability study, and a study of plume geometry, spray pattern, or droplet or particle size distribution for nasal spray products.

II.A.2.k. Bioequivalence requirement. We are proposing to move the definition of “bioequivalence requirement” currently in § 320.1(f) to § 314.3(b), with a minor grammatical correction, for ease of reference and organizational convenience. The term “bioequivalence requirement” is relevant to matters covered in part 314 in addition to matters in part 320 and thus appropriate for inclusion in the general definition section for this part.

II.A.2.l. Commercial marketing. We are proposing to define “commercial marketing” to mean the introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA, outside the control of the ANDA holder, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale to parties identified in the approved ANDA.

This proposed definition is based on the use of this term in current § 314.107(c)(4); however, we are proposing to alter the scope of the exclusion for transfer of the drug product for reasons other than sale. Section 314.107(c)(4) currently provides that commercial marketing “does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder” (emphasis added). Our proposed definition is intended to clarify that the ANDA holder’s shipment of a drug product described in an approved ANDA to

any party named in the ANDA for purposes described in the ANDA (e.g., contract packaging) is not “commercial marketing” of the drug product even though such transfer arguably places the drug products outside of the control of the manufacturer for some period of time. However, shipment of the drug product to any other party or for any other purpose would not fall within this exception and would be considered “commercial marketing” (i.e., an introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA outside the ANDA holder’s control). For example, if the ANDA holder ships the drug product to a wholesaler, a repackager not identified in the ANDA, or directly to a pharmacy, hospital, health maintenance organization, or other like entity, the ANDA holder will have commercially marketed the product as of the date of its shipment (if the ANDA holder complies with the notification requirement described in proposed § 314.107(c)(2)).

The first commercial marketing of a drug is discussed in section II.A.2.a (definition of the 180-day exclusivity period).

II.A.2.m. Component. We are proposing to add the definition of “component” currently in § 210.3(b)(3) to § 314.3(b) without changes. The term “component” is used within the defined term “active ingredient” and thus is appropriate for inclusion in the general definition section for this part (see section II.A.2.e).

II.A.2.n. Date of approval. We are proposing to move the definition of “date of approval” currently in § 314.108(a) to § 314.3(b) with several revisions. These proposed revisions to the definition of “date of approval” are not intended to alter our interpretation of § 314.108.

Our proposed revisions to the definition of “date of approval” incorporate use of the term “approval letter,” which also is defined in § 314.3(b), and broaden the definition to include the

date of approval for an ANDA. In addition, we are proposing to remove from the definition of “date of approval” the caveat that the date of approval is the date on the approval letter “whether or not final printed labeling or other materials must still be submitted as long as approval of such labeling or materials is not expressly required” (§ 314.108(a)). This qualification is inapplicable to the date of approval of an ANDA because final printed labeling is required as a condition of approval (see §§ 314.94(a)(8) and 314.127(a)(7)). With respect to NDAs (including 505(b)(2) applications), § 314.105(b) specifically addresses the circumstances under which FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling, and it is unnecessary to summarize this approach in the definition of “date of approval.”

As proposed for revision, the “date of approval” is the date on the approval letter from FDA stating that the NDA or ANDA is approved. The date of approval refers only to a final approval and not to a tentative approval. We note that the date on the approval letter generally appears on the last page containing the electronic signature (endorsement).

II.A.2.o. Dosage form. We are proposing to define “dosage form” to mean the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as (i) the physical appearance of the drug product, (ii) the physical form of the drug product prior to dispensing to the patient, (iii) the way the product is administered, and (iv) design features that affect frequency of dosing. This term has been commonly used by the Agency over the years in the context of implementing section 505(j) of the FD&C Act and part 314. However, except for the examples of dosage forms used in the definition of “drug product,” the term “dosage form” not been expressly defined in § 314.3(b).

The dosage form is generally determined based on the form of the product before dispensing to the patient (see Abbott Laboratories v. Young, 691 F. Supp. 462, 464 n. 1 (D.D.C.

1988) (“The final dosage form of a drug is the form in which it appears prior to administration to the patient”), remanded on other grounds, 920 F.2d 984 (D.C. Cir. 1990), cert. denied, 502 U.S. 819 (1991)). This is consistent with other factors such as physical recognition, dosing, and manner of administration that contribute to the determination of dosage form. Appendix C to the Orange Book lists the dosage form categories for currently marketed products.

II.A.2.p. Drug product. A “drug product” is a finished dosage form (for example, a tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. We are proposing to delete a similar definition of “drug product” in current § 320.1(b) when we move the definitions in § 320.1 to § 314.3(b), to reflect the fact that § 314.3(b) already includes a definition of drug product. Although the two definitions of “drug product” differ slightly in wording, we believe that they are functionally identical, so that this proposed revision is intended to eliminate redundancy but not result in any substantive change in our interpretation of part 320.

II.A.2.q. First applicant. The MMA defines the term “first applicant” for purposes of section 505(j)(5) of the FD&C Act (see section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act). We are proposing to add the statutory definition, with minor editorial changes and additional clarifying text, to § 314.3(b) to facilitate our continuing implementation of the 180-day exclusivity provisions of the FD&C Act. We are proposing to define “first applicant” in § 314.3(b) to mean an applicant that, on the first day on which a substantially complete ANDA containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug. We are proposing to delete the definition of “applicant submitting the first application” in current § 314.107(c)(2) because it is superseded by the

statutory definition (see section II.M.3). We note that an applicant may be a “first applicant” based on the submission of a paragraph IV certification in an amendment to an ANDA if other criteria are met.

We interpret the term “drug” in the statutory definition of “first applicant” to mean “drug product” as currently defined in § 314.3(b) (see section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act). Consistent with our longstanding practice, we note that different strengths of a drug product constitute different drug products. For example, different ANDA applicants seeking approval for different strengths of a drug product approved in a single NDA may each be first applicants with respect to a different strength of the drug product, if other applicable statutory and regulatory requirements are met (see Apotex, Inc. v. Shalala, 53 F. Supp. 2d 454 (D.D.C.), aff’d, 1999 U.S. App. LEXIS 29571 (D.C. Cir. 1999)). In addition, there may be multiple first applicants for a single drug product if more than one ANDA applicant first submitted a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification on the same day.

We have interpreted the statutory requirement for a first applicant to “lawfully maintain” a paragraph IV certification to mean that the ANDA applicant must, as a condition of retaining first applicant status, continue to lawfully assert that a relevant listed patent (i.e., at least one of the patents for which a paragraph IV certification qualified the ANDA applicant for first applicant status) is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug for which the ANDA is submitted (see Letter from G. Buehler, Director, Office of Generic Drugs, to ANDA Applicant regarding 180-day exclusivity for dorzolamide/timolol ophthalmic solution, Docket No. FDA-2008-N-0483-0017 at 5-6, available at <http://www.regulations.gov>) (Dorzolamide/Timolol Letter). This approach comports with

comments that we received on the interpretation of the phrase “lawfully maintained” in response to the Request for MMA Comments (see Docket No. FDA-2004-N-0062-0006 (comment submitted by the Pharmaceutical Research and Manufacturers of America (PhRMA)) at 3-5, available at <http://www.regulations.gov> (PhRMA MMA Comment); see also Docket No. FDA-2004-N-0062-0009 (comment submitted by Eli Lilly and Company) at 1-2, available at <http://www.regulations.gov> (Lilly MMA Comment)).

For example, if an ANDA applicant is sued for infringement of a patent that qualified the applicant for first applicant status and a court enters a final decision from which no appeal has been or can be taken that the patent is infringed (or signs a settlement order or consent decree in the action that includes a finding of infringement and does not permit market entry before patent expiration), the ANDA applicant can no longer lawfully maintain a paragraph IV certification with respect to the infringed patent (see Dorzolamide/Timolol Letter at 6). As discussed in section II.E.1, the ANDA applicant is required to submit an amended patent certification under § 314.94(a)(12)(i)(A)(3) (paragraph III certification) in these circumstances. In addition, an ANDA applicant can no longer lawfully maintain a paragraph IV certification when the patent expires or if an ANDA applicant changes its certification from a paragraph IV certification to a 505(j)(2)(A)(viii) statement (see proposed § 314.94(a)(12)(viii)(C) and (D); see also Dorzolamide/Timolol Letter at 6, note 5).

It should be noted that an amendment to a substantially complete ANDA does not mean that the ANDA is no longer substantially complete or that a first applicant has not lawfully maintained its paragraph IV certification (unless the amendment requires a new patent certification and the amended patent certification is not a paragraph IV certification). However, if a first applicant submits several major amendments to its ANDA, there is a risk that the

applicant may not be able to obtain tentative approval within 30 months after the date on which the ANDA is filed, thereby forfeiting its eligibility for any 180-day exclusivity period (see section 505(j)(5)(D)(i)(IV) of the FD&C Act).

We note that certain definitions, such as the definition of “first applicant,” may be revised or supplemented in the future as we continue to implement the 180-day exclusivity provisions of the MMA.

II.A.2.r. Inactive ingredient. We are proposing to add the definition of “inactive ingredient” currently in § 210.3(b)(8) to § 314.3(b) without changes. The term “inactive ingredient” is relevant to matters covered in part 314 in addition to matters in part 210 and thus appropriate for inclusion in the general definition section for this part.

II.A.2.s. Listed drug. We are proposing to revise the definition of “listed drug” to clarify that a listed drug includes a drug product that is listed in the discontinued section of the Orange Book and that has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or 505(j)(6) of the FD&C Act or withdrawn from sale (irrespective of whether the NDA has been withdrawn) for what FDA has determined are reasons of safety or effectiveness. Accordingly, the proposed definition in § 314.3(b) would state that a listed drug is a new drug product that “has been approved” instead of one that “has an effective approval.” With respect to the exceptions to listed drug status, we are correcting the paragraph number in the reference to the statutory provision under which an ANDA may be withdrawn or suspended for reasons of safety or effectiveness (see section 505(j)(6) of the FD&C Act).

In addition, we are proposing conforming revisions to incorporate other changes we are proposing in this rulemaking regarding the distinction between approvals and tentative approvals

(see section II.K) and reliance upon the electronic version of the Orange Book (see section II.A.2.ee).

Listed drug status is evidenced by the drug product's identification in the current FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. However, we note that a drug product is deemed to be a listed drug on the date of the approval letter for the NDA or ANDA for that drug product, rather than the date on which the product is listed in the Orange Book.

II.A.2.t. Original application, original NDA. We are proposing to revise the definition of "original application" to include the alternate term "original NDA" for clarity and administrative efficiency. In addition, we are proposing to replace references to "application" with "NDA" for consistency with other changes in this proposed rulemaking. These minor revisions are not intended to substantively change the meaning of the term "original application."

II.A.2.u. Paragraph IV acknowledgment letter. We are proposing to define "paragraph IV acknowledgment letter" to mean a written, postmarked communication from the FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review (compare definition of "acknowledgment letter" discussed in section II.A.2.c). An acknowledgment letter or paragraph IV acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

The proposed definition of "paragraph IV acknowledgment letter" is intended to facilitate implementation of the MMA's timing requirements for notice to the NDA holder and each patent owner of a paragraph IV certification. A 505(b)(2) or ANDA applicant is required to send notice of its paragraph IV certification within 20 days after the date of the postmark on the paragraph

IV acknowledgment letter (see section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act and section II.D.1).

In response to the Request for MMA Comments, the Generic Pharmaceutical Association (GPhA) requested that FDA amend § 314.101(b)(2) to state that FDA will notify the applicant “in writing via a postmarked notice” that the ANDA has been received in light of the MMA’s timing requirements for notice of paragraph IV certification (see Docket No. FDA-2004-N-0062-0012 (comment submitted by GPhA) at 4-5, available at <http://www.regulations.gov>) (GPhA MMA Comment). Incorporation of the term “paragraph IV acknowledgment letter” in proposed § 314.101(b)(2) would address this concern with respect to ANDAs (see section II.J). In addition, although OGD currently sends a paragraph IV acknowledgment letter in an envelope bearing a postmark made by the U.S. Postal Service, we are proposing to broaden the definition the “postmark” to accommodate electronic transmissions in the future (see section II.A.2.y).

For ANDAs, OGD currently sends a “paragraph IV acknowledgment letter” to confirm the date on which the ANDA was received and to establish the timeframe within which an ANDA applicant must send notice of a paragraph IV certification contained in the original ANDA (see section II.D.1). The letter also provides ANDA applicants with an overview of the notice requirements associated with submission of a paragraph IV certification to a listed patent for the RLD.

For 505(b)(2) applications that rely on the Agency’s finding of safety and/or effectiveness for a listed drug and include a paragraph IV certification for a listed patent, the Notification of Issues Identified during the Filing Review (filing communication), sometimes referred to as the “74-day letter,” would constitute the “paragraph IV acknowledgment letter” defined in § 314.3. Unlike the paragraph IV acknowledgment letter for ANDAs, the OND filing

communication is typically sent in a franked envelope that may not bear a postmark made by the U.S. Postal Service. For purposes of § 314.52(b) and (c) (21 CFR 314.52(b) and (c)) only, the “date of the postmark” on the “paragraph IV acknowledgment letter” will be considered to be 4 calendar days after the date on which the filing communication is signed by the signatory authority (generally the Division Director or designee in the OND review division), which generally reflects the date on which the document is received by the U.S. Postal Service (see definition of “postmark” in proposed § 314.3). For example, if the filing communication is electronically signed by the Division Director or designee on Thursday, April 7th, the date of the postmark on the paragraph IV acknowledgment letter for the 505(b)(2) application, for purposes of § 314.52(b), would be Monday, April 11th. If OND sends the filing communication via electronic transmission in the future, then our proposed definition of “postmark” in § 314.3(b) would apply.

As noted previously, the paragraph IV acknowledgment letter triggers the requirements in proposed §§ 314.52(b) and 314.95(b) for sending notice of the paragraph IV certification. The proposed difference in interpreting the term “postmark” as applied to paragraph IV acknowledgment letters for 505(b)(2) applications reflects current OND practice regarding the mailing of filing communications, which should occur no later than 74 days after the date of submission of the 505(b)(2) application. In addition, although an indisputable date of mailing is needed for competing ANDAs that may be eligible for a period of 180-day exclusivity, a 505(b)(2) application does not raise these concerns. We invite comment on this proposed approach or whether an alternative approach should be considered.

II.A.2.v. Paragraph IV certification. We are proposing to define “paragraph IV certification” in § 314.3(b) to mean a patent certification of invalidity, unenforceability, or

noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4) for 505(b)(2) applications and ANDAs, respectively. This term is routinely used by the Agency and applicants to refer to this type of patent certification. The addition of the term “paragraph IV certification” to § 314.3(b) would provide a convenient means of clearly referencing the patent certification described in the section 505(b)(2)(A)(iv) and (j)(2)(A)(vii)(IV) of the FD&C Act and implementing regulations.

II.A.2.w. Patent owner. We are proposing to define “patent owner” as the owner of the patent for which information is submitted for an NDA. A patent may be owned by more than one person. If a patent owner seeks to have its designated representative receive notice of a paragraph IV certification by a 505(b)(2) or ANDA applicant that relies upon a listed drug claimed by the patent, the patent owner should ensure that current information regarding the correspondence address, in accordance with 37 CFR 1.33(d), is submitted to the PTO.

II.A.2.x. Pharmaceutical alternatives and pharmaceutical equivalents. We are proposing to revise the definition of “pharmaceutical equivalents” to clarify that this term is intended to refer to drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active ingredient. The requirement for pharmaceutically equivalent products to have the same route(s) of administration is consistent with FDA’s current practice, as described in section 1.2 of the preface to the Orange Book (33rd Edition, 2013, at vii). We are not proposing any changes to the definition of “pharmaceutical alternatives.”

We are proposing to move the definitions of “pharmaceutical alternatives” and “pharmaceutical equivalents” currently in § 320.1(c) and (d) to § 314.3(b), for ease of reference and organizational convenience. The concepts of “pharmaceutical alternatives” and “pharmaceutical equivalents” are relevant to matters covered in part 314 (including but not

limited to § 314.94 and proposed §§ 314.50(i)(1)(i)(C), 314.93(f), 314.96(c), and 314.97(b), discussed in section II.G.1-2, II.H, and II.I) in addition to matters in part 320 (21 CFR part 320).

II.A.2.y. Postmark. We are proposing to define the term “postmark” in § 314.3(b) to address the MMA’s requirement that a 505(b)(2) or ANDA applicant send notice of its paragraph IV certification within “20 days after the date of the postmark on the notice [i.e., the paragraph IV acknowledgment letter] with which [FDA] informs the applicant that the application has been filed” (see section 505(b)(3)(B)(i) and 505(j)(2)(B)(ii)(I) of the FD&C Act). The term “postmark” is not used elsewhere in section 505 of the FD&C Act or in our current regulations in part 314. In light of the transition by FDA and regulated industry to electronic communications, an interpretation of the term “postmark” to mean a postmark made by the U.S. Postal Service (“U.S. postmark”) could quickly become outdated. The purpose of the postmark in section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act is to establish a verifiable date from which the 20-day notice period runs. Accordingly, we are proposing a broader definition of a “postmark” to mean “an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the U.S. Postal Service or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the U.S. Postal Service or by a designated delivery service. For postmarks documenting an electronic event, the date of transmission is the date (in a particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender’s time zone that provides the controlling date of electronic transmission.” This proposed definition of “postmark” is adapted from the definition of “electronic postmark” in regulations issued by the Internal Revenue Service (IRS) with

respect to electronic filing of documents required under 26 U.S.C. 7502 (see 26 CFR 301.7502-1(d)(3)(ii)).

We invite comment on our proposed interpretation of the term “postmark” in the context of a paragraph IV acknowledgment letter from FDA to an applicant for a 505(b)(2) application or ANDA, and whether our regulations should be amended to define differently the specific date from which the 20-day notice period runs.

II.A.2.z. Reference standard. We are proposing to define “reference standard” as the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval. This proposed definition reflects the Agency’s longstanding use of this term, as described in the preamble to our 1992 final rule implementing the Hatch-Waxman Amendments (“FDA intends the reference listed drug to be the same drug product selected by the agency as the reference standard for bioequivalence determinations” (57 FR 17950 at 17954). By generally designating a single drug product as the standard to which generic versions must be shown to be bioequivalent, FDA seeks to avoid possible significant variations among generic drugs, which could result if such drugs were compared to different drug products.

The reference standard is identified in the Orange Book by the word “yes” in the “RLD” column. In certain circumstances, a drug product approved in an ANDA (including a petitioned ANDA) may be designated as the reference standard for bioequivalence studies intended to support approval of an ANDA. For example, if the RLD is a drug product approved in an NDA that has been withdrawn from marketing (for reasons other than safety or effectiveness), a therapeutically equivalent drug product approved in an ANDA may be designated as the reference standard.

We recognize that the term “reference standard” has other meanings, including in the context of part 314 (see § 314.50(e)(1)(C)) regarding submission of representative samples of reference standards used in analytical studies, excluding pharmacopoeial reference standards). The proposed definition of “reference standard” applies solely to the product used in conducting an in vivo bioequivalence study required for approval.

II.A.2.aa. Same drug product formulation. We are proposing to move the definition of “same drug product formulation” currently in § 320.1(g) to § 314.3(b), without changes, for ease of reference and organizational convenience. The term “same drug product formulation” is relevant to matters covered in part 314 (including but not limited to §§ 314.94 and 314.96) in addition to matters in part 320.

II.A.2.bb. Strength. We are proposing to define the term “strength” in § 314.3(b) to mean the amount of drug substance contained in, delivered, or deliverable from a drug product. The amount of drug substance contained in, delivered, or deliverable from a drug product includes: (i)(A) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure) and/or, as applicable (i)(B) the concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume). If these weights and measures are not applicable to a type of drug product or dosage form, then the strength of the drug product may be described by such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from the drug product. For example, the strength of certain drug-device combination products (such as a transdermal delivery system) may be expressed as the amount of drug substance delivered per unit time.

This proposed definition is intended to codify FDA’s interpretation of the term “strength” in the context of section 505(j)(2)(A)(iii) of the FD&C Act. This proposed definition also will facilitate implementation of certain statutory provisions added by the MMA regarding amendments and supplements that seek approval of a “different strength” (see section 505(b)(4)(B) and (j)(2)(D)(ii) of the FD&C Act). Different strengths of a drug product constitute different drug products.

The amount of the drug substance “delivered” from a drug product is intended to describe the mass of drug substance delivered to the patient either per unit time (e.g., as in transdermal delivery system) or per actuation (e.g., as in metered dose inhalers) and excludes excess drug substance that although not available for labeled use, is necessary to allow for the specified total delivery (e.g., a specified number of hours for a transdermal delivery system or a specified number of actuations for a metered dose inhaler).

The amount of drug substance “deliverable from” a drug product is intended to exclude the excess volume allowed by the U.S. Pharmacopeia (USP) (to permit withdrawal and administration of the labeled volume of an injectable product) from the description of the “strength” of the drug product (see 21 CFR 201.51(g)).

FDA has a longstanding history of considering a difference in the total quantity of drug substance of a parenteral product (e.g., a single or multiple dose vial) or a difference in the concentration of a parenteral product to be a difference in the “strength” of the product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act. FDA considers it important to review proposed differences in the total drug content or the concentration of a parenteral product because such changes can result in medication errors and incorrect dosing of patients. Accordingly, the strength of a parenteral drug product is determined by both criteria in paragraph

(i) of the proposed definition--i.e., the total quantity of drug substance in a container closure and the concentration of the drug substance.

For other dosage forms, the strength of the drug product is determined based only on the criteria in paragraph (i)(A) or (i)(B) of the proposed definition. For example, the strength of a solid oral dosage form is determined only by the total quantity of drug substance in a dosage unit (e.g., a 25-milligram (mg) tablet). In contrast, the strength of a semisolid dosage form is typically determined by the concentration of the drug substance. For example, the strength of a cream is generally expressed by the concentration as a weight/weight percentage reflecting the mass of the drug substance per unit mass of the drug product.

We recognize that the weights and measures described in paragraph (i) of the proposed definition may not be applicable to all types of drug product or dosage forms. Accordingly, paragraph (ii) of the proposed definition provides that the strength of the drug product may be described by such other criteria as the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from the drug product.

It should be emphasized that the proposed definition of strength refers to the amount of the drug substance (active ingredient), and not the amount of the active moiety, in the drug product. However, we recognize that approved drug products formulated with a salt of an acid or a base (commonly referred to as “salt drug products”) may use the active moiety in the name rather than the drug substance to conform with a drug product naming policy established by the USP. Although the USP naming policy describes the “strength” of a drug product as the amount of active moiety present in the product, the strength of the drug product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act is the amount of the drug substance. These approaches to describing the strength of the drug product do not conflict because if two drug products

containing the same drug substance are demonstrated to have the same “strength” in terms of active moiety, they will always have the same strength in terms of drug substance. For example, a tablet drug product that contains 125 mg of the drug substance “novelpril maleate” equivalent to 100 mg of the active moiety “novelpril” would be expressed as “novelpril tablet 100 mg.” Based on the proposed definition in § 314.3(b), the strength of the drug product is 125 mg of the drug substance “novelpril maleate.” The label for this product would describe both the “strength” expressed in terms of active moiety and the strength expressed in terms of drug substance. The Agency recognizes that this naming policy will result in situations in which the “strength” that directly follows the drug product name for such products will be expressed in terms of active moiety and not in terms of drug substance, and that this might be confusing. FDA seeks comment on this approach to the proposed definition of strength in light of these considerations.

We also generally invite comment on whether this proposed definition adequately encompasses the broad range of dosage forms and drug products to which a proposed definition of “strength” in § 314.3(b) would apply.

II.A.2.cc. Substantially complete application. The MMA defines the term “substantially complete application” for purposes of section 505(j)(5) of the FD&C Act (see section 505(j)(5)(B)(iv)(II)(cc) of the FD&C Act). We are proposing to define “substantially complete application” in § 314.3(b) to incorporate this statutory definition with minor editorial revisions. As proposed, a “substantially complete application” would mean an ANDA that on its face is sufficiently complete to permit a substantive review and contains all the information required under section 505(j)(2)(A) of the FD&C Act and § 314.94. For an application to be substantially complete, any information referenced in the application must have been provided to the Agency.

For example, FDA will refuse to receive an ANDA for which a referenced Drug Master File has not been submitted or that omitted relevant stability or bioequivalence data as of the date of submission of the ANDA. There may be other bases for finding that an application is not substantially complete--for example, electronic submissions that are not readable or do not follow FDA's recommendations for electronic application format may be determined to be not substantially complete and refused for receipt.

In addition, we are proposing conforming revisions to § 314.101(b) to clarify that receipt of an ANDA means that FDA has made a threshold determination that the ANDA is substantially complete (see section II.J). Our proposed replacement of the current criterion "sufficiently complete to permit a substantive review" with the synonymous term "substantially complete application" is not intended to alter the meaning. Rather, we are seeking to use defined terms consistently throughout our regulations.

II.A.2.dd. Tentative approval. The MMA defines the term "tentative approval" for purposes of section 505(j)(5) of the FD&C Act to mean "notification to an applicant by the Secretary that an [ANDA] meets the requirements of [section 505(j)(2)(A)], but cannot receive effective approval because the application does not meet the requirements of [section 505(j)(5)(B)], there is a period of exclusivity for the listed drug under [section 505(j)(5)(F)] or section 505A, or there is a 7-year period of exclusivity for the listed drug under section 527" (section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act). We are proposing to define "tentative approval" in § 314.3(b) to incorporate the statutory text and extend this general definition, with appropriate conforming revisions, to include tentative approval of an NDA (including a 505(b)(2) application).

Proposed § 314.3(b) defines “tentative approval” to mean the notification that an NDA (including a 505(b)(2) application) or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved because there is unexpired orphan drug exclusivity for a listed drug, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met, because there is a period of exclusivity for the listed drug under § 314.108 or section 505A of the FD&C Act (21 U.S.C. 355a), or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the application may be approved no earlier than the date specified. Proposed § 314.107(b)(4) describes the circumstances in which FDA will issue a tentative approval letter (see section II.M.2.d).

The proposed definition of “tentative approval” clarifies that a drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA (compare section 505(j)(5)(B)(iv)(II)(dd)(BB) of the FD&C Act). We have proposed minor editorial revisions to the limitation described in the statute to replace references to “effective approval” of an NDA or ANDA with language reflecting our current practice. As discussed in section II.K, the Agency does not issue approval letters with delayed effective dates.

II.A.2.ee. The list. We are proposing to revise the definition of “the list” to mean the list of approved drug products published in FDA’s current “Approved Drug Products With Therapeutic Equivalence Evaluations,” available electronically on FDA’s Web site (<http://www.fda.gov/cder>). These clarifying revisions reflect our longstanding practice of relying upon the electronic version of the Orange Book (currently available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>), which is updated on a regular basis

and can be accessed from FDA's Web site. We are proposing to delete the words "current edition," "any current supplement," and "publication" from the definition as these phrases imply reference to a printed version. As discussed in section II.B.3, the Agency no longer arranges for publication of an annual printed edition or monthly printed supplements to the Orange Book.

Although the format of the electronic version of the Orange Book may change with advances in technology, FDA intends to maintain a publicly available version of the list that includes, among other things: Approved NDAs and ANDAs; therapeutic equivalence evaluations (as applicable); exclusivity granted to a listed drug; patents submitted for listing by the NDA holder; use codes for method-of-use patents; requests to remove a patent from the list; and, upon request on a prospective basis, the date on which patents are received by FDA for listing.

II.A.2.ff. Therapeutic equivalents. We are proposing to define "therapeutic equivalents" as approved drug products that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions of use specified in the labeling. This proposed definition reflects the Agency's longstanding interpretation of this term as set forth in section 1.2 of the preface to the Orange Book (33rd Edition, 2013, at vii).

II.A.3. Proposed Amendments to Definitions in Current § 314.108

As discussed in sections II.A.1, II.A.2.f, and II.A.2.n, we are proposing to move the definitions of the terms "active moiety" and "date of approval" from § 314.108(a) to § 314.3(b). We are proposing to amend § 314.108 to state that the definitions in § 314.3 (in addition to other definitions in § 314.108) apply to § 314.108.

We also are proposing to add a definition of “bioavailability study” to § 314.108(a) to clarify the scope of this term as used in section 505(c)(3)(E)(iii), (c)(3)(E)(iv), (j)(5)(F)(iii), and (j)(5)(F)(iv) of the FD&C Act and § 314.108(b)(4) and (b)(5) regarding certain exclusivity determinations. The FD&C Act provides that a “bioavailability study” is not a type of “new clinical investigations ... essential to the approval of the application [or supplement] and conducted or sponsored by the applicant” eligible for a 3-year period of exclusivity during which a 505(b)(2) application or ANDA may not be approved for the same conditions of approval (see section 505(c)(3)(E)(iii), (c)(3)(E)(iv), (j)(5)(F)(iii), and (j)(5)(f)(iv) of the FD&C Act; see also § 314.108(b)(4) and (b)(5)).

The proposed definition of “bioavailability study” means a study to determine the bioavailability or the pharmacokinetics of a drug. This definition incorporates by reference the revised definition of “bioavailability” proposed in § 314.3. This proposed revision is intended to clarify that a pharmacokinetic study, which generally is conducted in the same manner as a bioavailability study, also is not eligible for 3-year exclusivity. Although not specifically defined in part 314, the term “pharmacokinetics” is generally understood to refer to the way a drug is handled by the body, which is described by pharmacokinetic measures (such as area under the curve and concentration at the maximum) and other derived measures (such as clearance, half-life, and volume of distribution). The values of these measures reflect the absorption (A), distribution (D), and elimination (E) of a drug from the body. A drug can be eliminated by both metabolism (M) to one or more active and inactive metabolites and excretion of the unchanged drug. The overall set of processes is often referred to as ADME, which ultimately controls systemic exposure to a drug and its metabolites after drug administration.

II.A.4. Definitions in Current §320.1

We are proposing to move the definitions in current § 320.1(a) through (g) to § 314.3(b). We are proposing this change for ease of reference because certain terms defined in current § 320.1 already are set forth in other parts of our regulations (e.g., “bioequivalence”). Proposed § 320.1 would simply state that the definitions in § 314.3(b) apply to part 320.

II.B. Submission of Patent Information (Proposed § 314.53)

II.B.1. General Requirements for Submission of Patent Information (Proposed § 314.53(b) and (c))

Section 314.53(b) of our regulations requires that an applicant submitting an NDA (including a 505(b)(2) application), an amendment to an NDA, or, except as provided in § 314.53(d)(2), a supplement to an approved application, submit the patent information described in § 314.53(c) on Forms FDA 3542a and 3542 with the filing or upon and after approval, respectively. The information provided in Form FDA 3542 for any patent which claims the drug or a method of using the drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug is published in the Orange Book after approval of the NDA or the supplement.

In the Federal Register of April 30, 2007 (72 FR 21266), we responded to comments submitted to FDA regarding FDA’s request for an extension of approval of the collection of information related to patent submission and listing requirements involving Forms FDA 3542a and 3542 (April 2007 notice). At that time, we made certain revisions to Forms FDA 3542a and 3542 and the instructions for completing those forms to clarify acceptable practices in accordance with our existing regulations. Other proposed changes to Forms FDA 3542a and

3542 would have required revisions to the regulations upon which the requirements in Forms FDA 3542a and 3542 are based. In sections II.B.1.a and II.B.2.a, we propose certain revisions to the content of patent information submitted to FDA and the circumstances under which submission of patent information is required. These changes to the required submission of patent information are intended to clarify the basis for requiring certain information, revise and streamline our requirements, and describe acceptable approaches to compliance with applicable regulations.

Table 2 summarizes the proposed changes related to reporting requirements for submission of patent information:

Table 2.--Highlights of Proposed Changes Regarding Patent Reporting Requirements¹

Current Regulations	Proposed Revisions to Regulations
<u>General Requirements (§ 314.53(c)(1))</u> Patent information will not be accepted unless it is complete and submitted on the appropriate forms (Form FDA 3542a or 3542).	<u>General Requirements (§ 314.53(c)(1))</u> <ul style="list-style-type: none"> Patent information will not be accepted unless it is submitted on the appropriate forms (Form FDA 3542a or 3542) and contains the information required in § 314.53(c)(2).
<u>Reporting Requirements (§ 314.53(c)(2))</u> The required information and verification in § 314.53(c)(2)(i) and (c)(2)(ii) includes: <ul style="list-style-type: none"> Information on whether the patent has been submitted previously for the NDA. Information on whether the drug substance patent claims a polymorph that is the same active ingredient that is described in the pending NDA or supplement, and, if so, has test data described in § 314.53(b)(2). 	<u>Reporting Requirements (§ 314.53(c)(2))</u> The required information and verification in § 314.53(c)(2)(i) and (c)(2)(ii) includes: <ul style="list-style-type: none"> Information on whether the patent is a re-issued patent of a patent submitted previously for listing for the NDA or supplement. Information on whether the drug substance patent claims <u>only</u> a polymorph that is the same active ingredient that is described in the pending NDA or supplement, and, if so, has test data described in § 314.53(b)(2).

Table 2.--Highlights of Proposed Changes Regarding Patent Reporting Requirements¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Method-of-Use Patents (§ 314.53(c)(2)(i)(O) and (c)(2)(ii)(P))</u></p> <p>The required information and verification in § 314.53(c)(2)(i) and (c)(2)(ii) includes</p> <ul style="list-style-type: none"> Information on each method-of-use patent including the following: <ul style="list-style-type: none"> (2) Identification of the specific section of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted (3) The description of the patented method of use as required for publication. 	<p><u>Method-of-Use Patents (§ 314.53(c)(2)(i)(O) and (c)(2)(ii)(P))</u></p> <p>The required information and verification in § 314.53(c)(2)(i) and (c)(2)(ii) includes:</p> <ul style="list-style-type: none"> Information on each method-of-use patent including the following: <ul style="list-style-type: none"> (2) Identification of the specific section(s) of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted (if the scope of the method-of-use claim(s) of the patent does not cover every use of the drug, the applicant must identify only the specific portion(s) of the indication or other condition of use claimed by the patent); (3) The description of the patented method of use as required for publication (which must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval).
<p>[No corresponding regulation]</p>	<p><u>Exceptions to Required Submission of Patent Information (§ 314.53(c)(2)(i)(S) and 314.53(c)(2)(ii)(T))</u></p> <ul style="list-style-type: none"> If the applicant submits information for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide information on whether that patent also claims the drug product (composition/formulation). If the applicant submits information for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide information on whether that patent also claims the drug substance (active ingredient). However, an applicant that submits information for a method-of-use patent must also submit information regarding whether that patent also claims either the drug substance or the drug product.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.B.1.a. Drug substance (active ingredient) and drug product (formulation or composition) patents. We are proposing to revise § 314.53(c)(1) to clarify that FDA accepts

patent information submitted on Form FDA 3542a or 3542, as appropriate, as long as the form contains the information required in § 314.53(c). The statement in our current regulations that FDA “will not accept the patent information unless it is complete ...” has generated confusion in some cases, particularly where a portion of the specific information requested in a section on FDA Form FDA 3542a or 3542 was not applicable to the patent for which the form was submitted. By proposing to revise § 314.53(c)(1) to state that we will not accept the patent information unless it “contains the information required in paragraph (c)(2) of this section,” we are clarifying that FDA will accept a submission of patent information on Form FDA 3542a or 3542, as appropriate, that omits patent information requested on the form where that omission is permitted under an exception in § 314.53(c)(2).

We are proposing to add § 314.53(c)(2)(i)(S) and (c)(2)(ii)(T) to describe exceptions to the required submission of patent information. Proposed § 314.53(c)(2)(i)(S)(1) and (c)(2)(ii)(T)(1) state that if a patent claims the drug substance that is the active ingredient in the drug product for which approval is sought or has been granted, respectively, and is eligible for listing in the Orange Book, it is not necessary for an applicant to provide information on whether the patent also claims the drug product. Similarly, we are proposing to add § 314.53(c)(2)(i)(S)(2) and (c)(2)(ii)(T)(2) to provide that if a patent claims the drug product for which approval is sought or has been granted, respectively, and is eligible for listing in the Orange Book, it is not necessary for an applicant to provide information on whether the patent also claims the drug substance that is the active ingredient in the drug product. These proposed revisions to our regulations provide that an applicant need only satisfy the requirements for patent listing set forth in section 505(b)(1) and (c)(2) of the FD&C Act and, subject to § 314.53(c)(2)(i)(O)(3) and (c)(2)(ii)(P)(4), discussed in this section of the document, need not

identify each basis on which the patent claims the drug. The designation of a patent as claiming the drug substance and/or drug product for purposes of listing in the Orange Book is not intended to define the scope of the patent claims that an NDA holder or patent owner may assert against a 505(b)(2) or ANDA applicant based on a listed patent.

Whether or not the applicant provides information stating that the patent claims the drug substance or the drug product, an applicant must submit information regarding whether the patent claims one or more methods of using the drug product for which approval is sought or has been granted (method-of-use patent). We are proposing to add § 314.53(c)(2)(i)(O)(3) and (c)(2)(ii)(P)(4) to confirm that the proposed exceptions to required submission of patent information do not alter the requirements for submission of method-of-use patent information. The information regarding method-of-use patents is required for implementation of the patent certification and statement provisions of the FD&C Act. Section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act provide that a 505(b)(2) and ANDA applicant, respectively, may submit a statement for a method-of-use patent which does not claim a use for which the applicant is seeking approval, instead of a patent certification under section 505(b)(2)(A)(iii) or 505(j)(2)(A)(vii)(III) of the FD&C Act (paragraph III certification) or a paragraph IV certification to the listed patent. Information on whether a patent claims the drug substance or drug product in addition to whether the patent claims one or more methods of use is required because a 505(b)(2) or ANDA applicant that avails itself of the statutory provision that permits it to not seek approval of a method of use claimed by the patent (and carve out from product labeling the method-of-use information claimed by the patent) would still be required to submit a patent certification with respect to any drug substance or drug product claims covered by the same listed patent (see Letter from Janet Woodcock, M.D., Director, CDER, to Rosemarie R.

Wilk-Orescan, Novo Nordisk Inc., and James F. Hurst, Winston & Strawn LLP, dated December 4, 2008, regarding Docket Nos. FDA-2008-P-0343-0009 and FDA-2008-P-0411-0006, available at <http://www.regulations.gov>) (Repaglinide Citizen Petition Response). For example, a 505(b)(2) or ANDA applicant may submit a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii), respectively, of the FD&C Act for a method-of-use patent that does not claim a use for which the applicant is seeking approval and a paragraph IV certification for any remaining drug substance, drug product, or other method-of-use claims covered by the same patent. This approach is sometimes described as a “split certification” to the patent.

We note that a 505(b)(2) or ANDA applicant that submitted a paragraph IV certification in addition to a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act must comply with the notice requirements for a paragraph IV certification and may be subject to a 30-month stay of approval if patent infringement litigation is initiated within the statutory timeframe. An ANDA applicant that submitted a paragraph IV certification and a statement pursuant to section 505(j)(2)(A)(viii) of the FD&C Act to a listed patent also may be eligible for 180-day exclusivity based on its paragraph IV certification if the applicant is a “first applicant” and meets other statutory and regulatory requirements.

II.B.1.b. Drug substance patents that claim only a polymorph of the active ingredient. Section 314.53(c)(2)(i)(M)(2) and (c)(2)(ii)(N)(2) currently require submission of information on whether the patent claims a polymorph (generally, a drug substance with a different crystalline (including solvates and hydrates) or amorphous form of the same drug substance) that is the same active ingredient as that described in the pending NDA, amendment, or supplement. We explained in the preamble to the June 2003 final rule that “it would be consistent to interpret ‘drug substance’ for patent submission and listing purposes as including certain drug substances

having different physical forms if they would be considered the same active ingredient for ANDA approval purposes” (68 FR 36676 at 36678).

We are proposing to revise these regulations to state that an applicant is only required to provide information on whether the patent claims a polymorph that is the same active ingredient described in the pending NDA, amendment, or supplement if the only basis on which the patent is eligible for listing is that it claims the polymorph. Based on comments received from industry on this issue (see April 2007 notice) and inquiries from applicants regarding completion of Forms FDA 3542a and 3542, we have tentatively concluded that our regulations need to be modified. With respect to a patent that claims the drug substance or drug product described in the pending NDA, amendment, or supplement and one or more polymorphic forms of the drug substance, an applicant is not required to provide information on whether the patent claims a polymorph if the patent otherwise meets the statutory requirements for submission of patent information regarding the drug substance or drug product.

Similarly, we are proposing to make conforming revisions to § 314.53(b)(1), (b)(2), (c)(2)(i)(M)(3), and (c)(2)(ii)(N)(3) to provide that the applicant certification regarding test data required by § 314.53(b) applies only to patents that claim only a polymorph. This provision also had generated confusion, and we are proposing revisions for clarification.

II.B.1.c. Method-of-use patents. Section 314.53(b)(1) currently states that an applicant “shall separately identify each pending or approved method of use and related patent claim.” This text has been subject to differing interpretations by applicants as to whether our regulations require submission of patent information (and completion of Forms FDA 3542a and 3542) on a claim-by-claim basis. In the June 2003 final rule, we explained that we require identification of individual patent claims for method-of-use patents to assist 505(b)(2) and ANDA applicants in

determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (see 68 FR 36676 at 36682 and 36685). In the April 2007 notice, we clarified that “consistent with our regulations at § 314.53(b)(1), ... an applicant may list together multiple patent claims for each pending or approved method of use. However, each pending or approved method of use must be separately identified and therefore will require separate listing(s) of method-of-use information in section 4 of Forms FDA 3542a and 3542. Therefore, if a patent claims one or more methods of use that apply to a pending application or approved product, each pending or approved method of use would need to be listed separately along with the patent claim number(s) for the patent claim(s) for the pending or approved method of use. A single Form FDA 3542a or Form FDA 3542, as appropriate, may be used to list a patent claiming more than one method of use, provided that each method of use is listed separately along with the patent claim number(s) for the patent claim(s) for the pending or approved method of use. This regulatory approach accomplishes the statutory objective of providing adequate information to permit ANDA and 505(b)(2) applicants to file statements which assert that the method-of-use patent does not claim a use for which the applicant is seeking approval” (72 FR 21266 at 21268).

We are proposing to revise § 314.53(b)(1) by replacing the word “claim” with “claim(s)” in the phrase “shall separately identify each pending or approved method of use and related patent claim.” This proposed revision is intended to further clarify that an applicant may list together multiple patent claims for a pending or approved method of use on Forms FDA 3542a and 3542, respectively. However, each pending or approved method of use must be separately identified and therefore will require separate listing(s) of method-of-use information in section 4 of Forms FDA 3542a and 3542.

We also are proposing to revise § 314.53(b)(1), (c)(2)(i)(O)(2), (c)(2)(ii)(P)(2) and (c)(2)(ii)(P)(3) to enhance compliance by NDA applicants with the requirements for identifying the specific section(s) of product labeling that correspond to the method of use claimed by the patent and, upon approval, describing the approved method of use claimed by the patent, as required for publication in the Orange Book. Proposed § 314.53(b)(1) would expressly require that if the scope of the method-of-use claim(s) of a patent does not cover every use of the drug, the applicant must identify only the specific sections of product labeling that correspond to the specific portion(s) of the indication or other condition of use claimed by the patent. The specific product labeling that corresponds to the protected use may appear in sections of the labeling other than “Indications and Usage.” This proposed revision and conforming revisions to proposed § 314.53(c)(2)(i)(O)(2) and (c)(2)(ii)(P)(2) would address situations in which the scope of the method of use claimed by the patent is narrower than the indication or other condition of use described in product labeling. In such cases, the NDA applicant must identify only the specific sections of product labeling that correspond to the portion(s) of the indication or other condition of use claimed by the patent and not the broader indication or other condition of use in the product labeling which may include, but not be limited to, the use claimed by the patent. Accurate identification of the specific sections of product labeling that correspond to the use claimed by the patent is necessary to enable FDA to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, which permit 505(b)(2) and ANDA applicants to omit protected conditions of use from labeling. This information regarding product labeling also is necessary for FDA to evaluate whether the omission of aspects of the listed drug’s labeling protected by patent would render the proposed drug product less safe or effective than the listed drug for all

remaining non-protected conditions of use and preclude approval (see § 314.127(a)(7); see also § 314.94(a)(8)(iv)).

Proposed § 314.53(c)(2)(ii)(P)(3) would codify our longstanding requirement that the NDA applicant's description of the patented method of use (the "use code") required for publication in the Orange Book must contain adequate information to assist FDA and 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. If the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder's "use code" must contain only the specific portion(s) of the indication or other method of use claimed by the patent. This requirement is necessary to effectively implement the statutory provisions that permit 505(b)(2) and ANDA applicants to submit a statement that the applicant is not seeking approval for the use claimed in the listed patent instead of a patent certification to the listed patent with respect to the method of use claim(s) (see section 505(b)(2)(B) and (j)(2)(C)(viii) of the FD&C Act, respectively). We require the NDA holder to submit an accurate description, subject to the verification requirements in § 314.53(c)(2)(ii)(R), of the method of use within the scope of the patent that claims an approved use of the drug to implement these statutory provisions. As the U.S. Supreme Court noted in Caraco Pharm. Labs. v. Novo Nordisk A/S: "An overbroad use code... throws a wrench into the FDA's ability to approve generic drugs as the statute contemplates" (132 S. Ct. 1670, at 1684 (2012)).

II.B.1.d. Patents previously submitted for listing. We are proposing to revise §§ 314.53(c)(2)(i)(J) and (c)(2)(ii)(K) to remove the requirement that an applicant provide information regarding whether the patent has been submitted previously for the NDA or supplement. This requirement was intended to assist the Orange Book staff with their

administrative listing responsibilities (see 68 FR 36676 at 36686). In response to a request for clarification of the purpose of this inquiry (see 72 FR 21266 at 21269) and to streamline the patent information submission requirements, we are proposing to revise §§ 314.53(c)(2)(i)(J) and (c)(2)(ii)(K) to request information on whether the patent is a reissuance of a patent submitted previously for listing in the Orange Book for the NDA or supplement, including the original patent number of the listed patent (see section II.B.1.e).

If a patent has been submitted previously for listing in the Orange Book, we currently request information on whether the expiration date is a new expiration date (§ 314.53(c)(2)(i)(K) and (c)(2)(ii)(L)). For example, a patent expiration date may be extended after NDA approval in response to a request for patent term restoration pursuant to 35 U.S.C. 156 (see proposed § 314.53(f)(2)(ii), discussed in section II.B.4.b). We are continuing to request this information.

We note that our proposed revisions to the patent information submission requirements for supplements to an approved NDA (see section II.B.2.a) are designed to identify, among other things, whether patents previously submitted for listing for the underlying NDA continue to claim the changed product as approved in the supplement.

II.B.1.e. Reissued patents. We are proposing certain revisions to our regulations to describe our requirements regarding submission of information related to patents that have been reissued by the PTO. Generally, a patent may be reissued to correct certain errors in the scope of claims or defects in a specification or drawing that otherwise would have invalidated, in whole or in part, the patent (see 35 U.S.C. 251). Accordingly, a reissued patent may affect both the patent certification or statement submitted by a 505(b)(2) or ANDA applicant and the infringement claims that could be asserted by the patent owner or NDA holder.

Although we recognize that the original patent is surrendered upon patent reissuance (see 37 CFR 1.178(a)), we are proposing to treat the original patent and the reissued patent as a “single bundle” of patent rights, albeit patent rights that may have changed with reissuance, for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity that relates to a paragraph IV certification to the original patent (see discussion in section II.E.4). FDA’s role in listing patents remains ministerial (see 59 FR 50338 at 50349, October 3, 1994 (1994 final rule); 68 FR 36676 at 36687 (June 2003 final rule)); however, we are mindful of the implications of reissued patents in fulfilling our statutory obligations regarding implementation of the patent certification and statement, 30-month stay, 180-day exclusivity, and tentative approval provisions of the FD&C Act. We are proposing these revisions to describe the responsibilities of an NDA applicant associated with listing a reissued patent. The requirements for a 505(b)(2) or ANDA applicant to provide an appropriate patent certification or statement to a reissued patent are discussed in section II.E.4).

We currently receive submissions of patent information for reissued patents and list those patents that are eligible for listing in the Orange Book. Reissued patents are identified by the PTO with the letters “RE” preceding the patent number and, because a patent is reissued for the unexpired part of the term of the original patent, have the same expiration date as the original patent. If the scope of claims was narrowed or broadened upon reissuance, the NDA applicant or holder may submit a reissued patent for listing in the Orange Book with a revised designation of whether the patent claims the drug substance, drug product, and/or a method or use, or with a revised use code.

Proposed § 314.53(c)(2)(i)(J) and (c)(2)(ii)(K) would provide that an NDA applicant or holder is required to include information on whether a patent submitted for listing is a reissuance of a patent previously submitted for listing for the NDA or supplement. Submission of patent information for reissued patents is subject to the 30-day timeframe for timely filed patent information set forth in section 505(c)(2) of the FD&C Act. As discussed further in section II.B.2.b, the timely filing of patent information for a reissued patent (including a reissued patent with a broadened scope of claims) does not alter the patent certification obligations of a 505(b)(2) or ANDA applicant whose application was pending when the original patent was filed by the holder of an approved application for listing more than 30 days after patent issuance (“late listed”). In other words, if a 505(b)(2) or ANDA applicant is not required to provide a patent certification or statement to the original patent pursuant to § 314.50(i)(4) or § 314.94(a)(12)(vi) because the patent was late listed, the 505(b)(2) or ANDA applicant would not be required to provide a patent certification or statement to the reissued patent even if timely filed following reissuance. This approach recognizes that the original and reissued patents comprise a “single bundle” of patent rights, which first became relevant to approval of 505(b)(2) applications and ANDAs with the submission of the patent information prior to reissuance. As described in section II.E.3, the date of submission of the original patent information also determines the availability of a 30-month stay arising from patent infringement litigation resulting from notice of a paragraph IV certification to the original or reissued patent (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

An original patent that has been reissued would remain listed in the Orange Book until FDA determined that any first ANDA applicant is no longer eligible for 180-day exclusivity or the 180-day exclusivity period has expired (see section II.E.4). We intend to designate original

patents that have been reissued and remain listed in the Orange Book for this reason with the suffix “*RE” based on information submitted by the NDA applicant or holder in accordance with § 314.53(c)(2)(ii)(K). In the absence of this designation, an applicant that submits an ANDA after a reissued patent is listed in the Orange Book may not provide a patent certification or statement with respect to the original patent. Instead, the ANDA applicant must provide a patent certification or statement to the reissued patent.

Should the scope of a reissued patent be narrowed such that it is no longer eligible for listing under section 505(b)(1) or 505(c)(2) of the FD&C Act, the NDA holder is required to request that the patent or patent information be removed from listing in the Orange Book (“patent delisting”), subject to the exceptions set forth in proposed § 314.53(f)(2) (see discussion in section II.B.4.b).

II.B.2. When and Where To Submit Patent Information (Proposed § 314.53(d))

Table 3 summarizes the proposed changes regarding when and where to submit patent information:

Table 3.--Highlights of Proposed Changes Regarding Submission of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
<u>Supplements (§ 314.53(d)(2)(i))</u> <ul style="list-style-type: none"> Applicant must submit patent information required under § 314.53(c) for a patent that claims the drug, drug product, or method of use for which approval is sought in a supplement: <ul style="list-style-type: none"> (A) to change the formulation; (B) to add a new indication or other condition of use; (C) to change the strength; (D) to make any other patented change regarding the drug, drug product, or method of use. 	<u>Supplements (§ 314.53(d)(2)(i))</u> <ul style="list-style-type: none"> Applicant must submit patent information required under § 314.53(c) for a patent that claims the drug substance, drug product, or method of use for which approval is sought in a supplement: <ul style="list-style-type: none"> (A) to change the dosage form or route of administration; (B) to change the strength; or (C) to change the drug product from prescription to OTC use.

Table 3.--Highlights of Proposed Changes Regarding Submission of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Supplements (§ 314.53(d)(2)(ii))</u> If an applicant submits a supplement for a change described in § 314.53(d)(2)(i), the following patent information submission requirements apply:</p> <ul style="list-style-type: none"> • If previously submitted patent information claims the changed product, the applicant must submit a certification with the supplement identifying the patents that claim the changed product. • If no patents, including previously submitted patents, claim the changed product, it must so certify. 	<p><u>Supplements (§ 314.53(d)(2)(ii))</u> If an applicant submits a supplement for a change other than one described in § 314.53(d)(2)(i), the following patent information submission requirements apply:</p> <ul style="list-style-type: none"> • If previously submitted patent information claims the changed product, the applicant is not required to resubmit this patent information unless the description of the patented method of use would change upon approval of the supplement, and FDA will continue to list this patent information for the product; • If previously submitted patent information no longer claims the changed product, the applicant must submit a request to remove that patent information from the list at the time of approval of the supplement; • If one or more existing drug substance, drug product, or method-of-use patents claim the changed drug product for which approval is sought in the supplement and such patent information has not been submitted to FDA, the applicant must submit the patent information required under § 314.53(c).

Table 3.--Highlights of Proposed Changes Regarding Submission of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Patent information deadline (§ 314.53(d)(3))</u></p> <ul style="list-style-type: none"> If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant must submit to FDA the required patent information within 30 days of the date of patent issuance. <p><u>Late submission of patent information (§§ 314.50(i)(4) and 314.94(a)(12)(vi))</u></p> <ul style="list-style-type: none"> [Provision directed to submission of required patent information in general.] 	<p><u>Newly issued patents (§ 314.53(d)(3))</u></p> <ul style="list-style-type: none"> If a patent is issued for a drug substance, drug product, or method of use after an NDA is approved, the applicant must submit to FDA the required patent information within 30 days of the date of patent issuance. If the required patent information is not submitted within 30 days of patent issuance, FDA will list the patent, but patent certifications will be governed by the provisions regarding untimely filed patents at §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii). <p><u>Untimely filing of patent information (§§ 314.50(i)(4) and 314.94(a)(12)(vi))</u></p> <ul style="list-style-type: none"> Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if: <ul style="list-style-type: none"> --the amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or --the amendment is submitted more than 30 days after a corresponding change in approved product labeling.
<p><u>Copies (§ 314.53(d)(4))</u></p> <ul style="list-style-type: none"> Applicant must submit an archival copy and a copy for the chemistry, manufacturing, and controls (CMC) section of the review copy to the CDER Central Document Room. Applicant must submit patent information by letter separate from, but at the same time as, submission of the supplement. 	<p><u>Submission of Forms FDA 3542a and 3542 (§ 314.53(d)(4))</u></p> <ul style="list-style-type: none"> Applicant must submit patent information required by § 314.53(c)(1) and (c)(2)(i), § 314.50(h), or § 314.70(f) on Form FDA 3542a to the CDER Central Document Room at the address identified on FDA's Web site. <ul style="list-style-type: none"> Form FDA 3542a should not be submitted to the Orange Book Staff in the Office of Generic Drugs. Applicant must submit patent information required by § 314.53(c)(1) and (c)(2)(ii) on Form FDA 3542 to the Office of Generic Drugs, Document Room, Attention: Orange Book Staff.

Table 3.--Highlights of Proposed Changes Regarding Submission of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
<u>Submission date (§ 314.53(d)(5))</u> <ul style="list-style-type: none"> Patent information will be considered submitted to FDA as of the date the information is received by the Central Document Room. 	<u>Submission date (§ 314.53(d)(5))</u> <ul style="list-style-type: none"> Patent information will be considered submitted to FDA for purposes of § 314.53(d)(3) as of the earlier of the date the information submitted on Form FDA 3542 is date-stamped by the Office of Generic Drugs, Document Room, or officially received electronically by FDA through the Electronic Submissions Gateway.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.B.2.a. Submission of patent information for NDA supplements (proposed § 314.53(d)(2)). We are proposing to revise the requirements for submission of patent information for NDA supplements to reduce duplicative submissions of patent information and enhance efficiency.

Section 314.53(c) requires submission of patent information for certain types of supplements that relate to the drug product or a method of using the drug product, namely those supplements that seek approval to change the formulation, add a new indication or other condition of use, change the strength, or make any other patented change regarding the drug, drug product, or any method of use (see § 314.53(d)(2)(i)(A) through (d)(2)(i)(D)). This approach avoided unnecessary resubmission of patent information with supplements that did not involve a change to the drug product or a method of using the product or involved a change that could not be patented (see 54 FR 28872 at 28910, July 10, 1989; and 59 FR 50338 at 50344). We are proposing to eliminate certain of these patent information submission requirements for supplements that seek approval for a change to an approved product and for which existing patents listed in the Orange Book for the specific drug product that is the subject of the supplement continue to claim the changed product (see proposed § 314.53(d)(2)(ii)(A)). These proposed revisions to our regulations also address a comment submitted by an association

representing research-based pharmaceutical and biotechnology companies that “submission of Forms FDA 3542a and 3542 with submission and upon approval, respectively, of an NDA supplement is redundant where the information has not changed since the form last was filed, imposes a burden on sponsors, and serves no statutory purpose” (72 FR 21266 at 21270).

Our proposed revisions to § 314.53(d)(2) would create two broad categories of supplements for purposes of patent information submission based on whether the supplement is a type for which approval would result in a new entry in the Orange Book. For supplements that seek approval for a change that will result in a new entry in the Orange Book (e.g., a change to the dosage form, route of administration, strength (including changes to concentration or total drug content), or prescription drug status (i.e., change the drug product from prescription use to over-the-counter (OTC) use)), an applicant must continue to submit patent information required under § 314.53(c) with submission of the supplement and following approval, respectively. Although these types of changes may not necessarily result in a submission of different patent information, by requiring an NDA holder to submit complete patent information for a supplement that, if approved, would result in a new entry in the Orange Book, we ensure that patent information listed for the new entry clearly expresses the NDA holder’s view regarding which patent(s) claim the drug or a method of using the drug as approved in the supplement. For example, different strengths of a drug product may have different patent coverage with respect to method-of-use patents that claim a dosing regimen or indication. In such a case, patent information would be required to be submitted with the filing of the NDA supplement and would be required to be submitted upon approval of the NDA supplement. This submission of patent information on Forms FDA 3542a and 3542 would, among other things, identify with specificity the new method of use claimed by the patent with reference to the proposed or approved

labeling, respectively, for the drug product. If the patents listed for the approved NDA also claim the drug or method of using the drug for which approval is sought in the NDA supplement, we will permit an applicant to submit a statement declaring that the patents currently listed for a specific NDA (identified by NDA number and product number as listed in the Orange Book) also claim the drug or method of using the drug for which approval is sought in the NDA supplement, if this statement is accompanied by the signed patent declaration verification required by § 314.53(c)(2)(i)(Q) and (c)(2)(ii)(R) and if patent information required by § 314.53(c)(2)(ii) previously was submitted (see June 2003 final rule (68 FR 36676 at 36681)). This proposed approach fulfills the statutory requirements for patent listing set forth in section 505(b)(1) and (c)(2) of the FD&C Act and ensures that patents listed for separate entries for drug products in the Orange Book are supported by an unambiguous submission of applicable patent information.

It should be noted that proposed § 314.53(d)(2)(i)(A) is intended to encompass only the types of changes in dosage form or route of administration that may be submitted as an NDA supplement and does not apply to proposed changes in dosage form or route of administration that should be submitted as a separate application (see guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees” (December 2004), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>) (Separate Marketing Application Guidance). Similarly, we note that proposed § 314.53(d)(2)(i)(C) describes supplements to change the drug product from prescription use to OTC status for all conditions of use, because a separate marketing application would be required for a change to OTC status for fewer than all conditions of use.

Our proposal would eliminate the automatic requirement for submission of patent information with a supplement seeking approval for a change in formulation or new indication or other condition of use (except for those conditions of use described in § 314.53(d)(2)(i)). However, new submission of patent information would still be required if the patent(s) that claim the product as changed by the supplement differ from the patent(s) currently listed for the drug product. For supplements that seek approval for a change to a listed product that would not result in a new entry in the Orange Book (i.e., a change other than one of the changes described in proposed § 314.53(d)(2)(i)), an applicant needs to evaluate whether each patent for which information is currently listed in the Orange Book for the drug product continues to claim the changed product. If existing patents listed for the product approved in the original application claim the product as changed by the supplement, the applicant is not required to resubmit this patent information unless the description of the method of use claimed by a patent would change upon approval of the supplement (see proposed § 314.53(d)(2)(ii)(A)). (In this regard, we note that an untimely filed patent that claims the product approved in the original application cannot be transformed into a timely filed patent with submission of a supplement.)

If, however, a listed patent no longer claims the product as changed by the supplement (e.g., a new formulation is no longer claimed by a patent listed for the original formulation of the drug product), then the applicant must submit a request to correct or remove the patent information from the list in accordance with proposed § 314.53(f)(2) at the time of approval of the supplement. Correspondingly, if one or more existing patents claim the product as changed by the supplement (e.g., a supplement seeking approval for a new indication) and this patent information has not been submitted to FDA, the applicant must submit the patent information with the supplement and following approval. The requirement in proposed § 314.53(d)(2)(ii)(C)

also would apply to submission of patent information for a patent currently listed for the drug as approved in the original application that claims the drug approved in the supplement in a new way (e.g., a new or additional method of use) and for which the patent information would be required to be submitted under § 314.53(c). In this case, the applicant would be required to comply with § 314.53(c) and submit patent information describing the new or additional method of use claimed by the patent with the supplement and following approval.

As noted previously in this section of the document, the Agency has received comments criticizing as redundant the requirement for submission of Forms FDA 3542a and 3542 with submission and upon approval, respectively, of an NDA supplement where the information has not changed since the form last was filed (see April 2007 notice). Section 505(b)(1) of the FD&C Act requires the submission of patent information with the filing of a supplement to an NDA. To the extent that patents currently listed for the drug product continue to claim the product as changed by the supplement, we interpret the statute to not require resubmission of duplicative patent information. In circumstances other than those described in proposed § 314.53(d)(2)(ii)(A), an applicant or sponsor must submit required patent information with submission and upon approval of a supplement. This requirement facilitates the prompt listing of patent information postapproval by requiring applicants to complete their initial assessment of relevant patents with submission of their application and during the pendency of its review.

We are proposing a conforming revision to § 314.70(f) to clarify that an applicant that submits a supplement to an NDA (including a 505(b)(2) application) also must comply with the patent information requirements under § 314.53.

II.B.2.b. Untimely filing of patent information (proposed §§ 314.53(d)(3), 314.50(i)(4), and 314.94(a)(12)(vi)). We are proposing to supplement § 314.53(d)(3) to expressly describe

our longstanding practice with respect to listing untimely filed patents. Proposed § 314.53(d)(3) states that if the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications will be governed by the provisions regarding untimely filed patents in §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii) of this part. We also are proposing to revise §§ 314.50(i)(4) and 314.94(a)(12)(vi) to include certain amendments to the description of the approved method(s) of use claimed by the patent within the category of untimely filed patent information.

Section 505(c)(2) of the FD&C Act requires an NDA holder to file patent information for a patent issued after the date of approval of the application within 30 days of patent issuance. (As clarified in proposed § 314.53(c)(2)(ii), this statutory requirement for timely filing does not apply to patent information submitted prior to approval of an NDA or supplement, even if the patent information is submitted to FDA more than 30 days after the patent is issued by the PTO.)

Section 505(c)(2) of the FD&C Act further directs the Agency to publish information on the newly-issued patent upon its submission, and we have interpreted this statutory provision to require listing in the Orange Book irrespective of whether the patent information has been timely filed. Although we list untimely filed patents pursuant to section 505(c)(2) of the FD&C Act, we generally do not require an applicant with a pending 505(b)(2) application or ANDA to provide a patent certification to a patent for which the NDA holder failed to comply with the statutory timeframe for submission of patent information after approval. Accordingly, the untimely filed patent will neither delay approval of a pending 505(b)(2) application or ANDA until patent expiration nor necessitate a carve-out of information related to a patented method of use.

Although an applicant with a pending 505(b)(2) application or ANDA that references the drug product generally would not be required to submit a patent certification to an untimely filed

patent that was late-listed as to the pending 505(b)(2) application or ANDA, we would permit an applicant to submit and maintain a patent certification (including a paragraph IV certification) or a statement pursuant to section 505(b)(2)(B) or 505(j)(2)(B)(viii) of the FD&C Act, if desired. For example, a 505(b)(2) or ANDA applicant may wish to submit a paragraph IV certification to challenge the late-listed patent and obtain patent certainty (i.e., determine whether the NDA holder or patent owner will initiate a patent infringement action against the applicant) instead of possibly marketing at risk.

We also are proposing to revise §§ 314.50(i)(4) and 314.94(a)(12)(vi) to state that, except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if:

- The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling or
- the amendment is submitted more than 30 days after a corresponding change in approved product labeling.

This proposed revision is consistent with the objective of ensuring that prospective 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug. In addition, proposed §§ 314.50(i)(4) and 314.94(a)(12)(vi) would complement proposed revisions to § 314.53 that are intended to enhance NDA holders' compliance with the requirement to accurately identify the specific sections of product labeling that correspond to the use claimed by the patent (see section II.B.1.c). If an amendment to change the patent use code is not related to a corresponding change in approved product labeling and is submitted more than 30 days after patent issuance (or patent reissuance), then the patent information is properly

considered untimely filed. In accordance with §§ 314.50(i)(4) and 314.94(a)(12)(vi), an untimely filed method-of-use patent does not require a patent certification or statement and would not delay approval of a pending 505(b)(2) application or ANDA. Similarly, if an amendment to change the patent use code is submitted more than 30 days after a corresponding change in approved product labeling, then the amendment lacks a clear temporal or substantive link to the specific section(s) of approved product labeling claimed by the patent, and the patent information is untimely filed.

An applicant with a pending 505(b)(2) application or ANDA that seeks to confirm that a newly listed patent was untimely filed (and may not require a patent certification in accordance with § 314.50(i)(4) or § 314.94(a)(12)(vi)) should contact the Orange Book staff. Irrespective of whether the patent was untimely filed (and thus late-listed as to the pending 505(b)(2) application or ANDA) or timely filed (and thus “later listed” as to the pending 505(b)(2) application or ANDA), a paragraph IV certification submitted for a patent filed with FDA after the date on which a 505(b)(2) application or ANDA (that is later determined to be substantially complete) was submitted will not give rise to a 30-month stay (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act and section II.G).

We note, however, that a 505(b)(2) application or ANDA submitted after the untimely filed patent is listed in the Orange Book is required to submit an appropriate patent certification or statement to the patent. As we explained in the 1994 final rule, “[t]he approach adopted by the Agency as best embodying the compromise adopted by Congress requires that if an NDA applicant submits required patent information on an approved drug product more than 30 days after issuance of the patent, FDA will publish the untimely information, but will not require ANDA and 505(b)(2) applicants with pending applications that have previously submitted a

certification, i.e. those applicants that would be prejudiced by the late submission, to recertify to the new patent. Only applicants that initially submit ANDA's or 505(b)(2) applications after the submission of the patent information or whose pending applications do not contain a valid certification at the time of submission would be required to submit a certification as to that patent. ... While this could result in two categories of ANDA's for a pioneer drug, those without certifications for the late-filed patent and those with certifications for that patent, this approach is the best means for discouraging manipulation of the patent filing scheme and providing optimum notice of applicable patents" (59 FR 50338 at 50340, response to comment 7).

We remind NDA holders that patents issued after approval of a drug under section 505(c) of the FD&C Act include reissued patents (see section II.B.1.e) as well as patents that claim a drug product listed in the discontinued section of the Orange Book. With reference to the latter category, we note that a 505(b)(2) or ANDA applicant may rely upon a drug product listed in the discontinued section of the Orange Book to the extent that the product was not withdrawn for reasons of safety or effectiveness (see § 314.151 with respect to ANDAs). Accordingly, we encourage NDA holders to ensure that they continue to comply with the statutory requirements for patent listing for products that have been discontinued from marketing.

We also are proposing to revise § 314.50(i)(4) to remove an incorrect reference to the possible submission of a certification under § 314.50(i)(1)(ii) after the NDA holder's untimely filing of patent information. If a 505(b)(2) applicant is required to submit a patent certification to untimely filed patent information as provided in proposed § 314.50(i)(4), a "no relevant patents" statement under § 314.50(i)(1)(ii) would not be an acceptable patent certification.

Finally, we are proposing to revise the heading for § 314.53(d)(3) to "newly issued patents" to better characterize the text and emphasize its applicability to patents issued after

approval of an NDA or supplement. We also are proposing to revise the heading for proposed §§ 314.50(i)(4) and 314.94(a)(12)(vi) to “untimely filing of patent information” and to make conforming revisions to the text of these sections for consistent use of terminology.

II.B.2.c. Where to send submissions of Forms FDA 3542a and 3542 (proposed § 314.53(d)(4)). We are proposing to require that patent information filed on Form FDA 3542 upon and after approval of an NDA or supplement be submitted directly to the Orange Book staff through the OGD Document Room. The Orange Book staff will send an archival copy of this patent information to CDER’s Central Document Room for filing with the NDA.

Our proposal to require that NDA holders submit post-approval patent information directly to the Orange Book staff is intended to facilitate prompt listing of patent information in the Orange Book after Form FDA 3542 has been officially received by the Agency. Currently, many NDA holders submit a duplicate or courtesy copy of Form FDA 3542 to the Orange Book staff electronically or via facsimile at the time of their submission of Form FDA 3542 to CDER’s Central Document Room. This patent information is listed in the Orange Book upon receipt by the Orange Book staff, and the Orange Book explains that the date on which patent information is published “may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).” However, this practice may result in publication of patent information prior to receipt by the official repository identified in our regulations and cause confusion for prospective first applicants and applicants with a pending 505(b)(2) application or ANDA seeking to determine whether or not the patent is late-listed. Proposed § 314.53(d)(4) designates the OGD Document Room as an official repository for submissions of Form FDA 3542, and proposed § 314.53(d)(5) (see section II.B.2.d) clarifies that the submission date of patent information provided by an NDA holder after approval of an application is the earlier of the date on which Form FDA 3542

is date-stamped by the OGD Document Room or officially received electronically by FDA through the Electronic Submissions Gateway. These proposed revisions to the regulations are intended to enhance efficiency and ensure that patent information is promptly listed after its receipt.

We note, however, that patent information submitted on Form FDA 3542a with the filing of an NDA, amendment, or supplement, and prior to approval of the application must continue to be submitted directly to the NDA as required by § 314.50(h) or § 314.70(f), as appropriate. An applicant should not submit a copy of Form FDA 3542a to the Orange Book staff; the Orange Book staff should only receive patent information submitted after approval of the NDA or supplement. An applicant should not submit a copy of the patent to FDA with submission of Form FDA 3542a or 3542.

II.B.2.d. Submission date of patent information (proposed § 314.53(d)(5)). We are proposing to revise § 314.53(d)(5) to clarify, for purposes of § 314.53(d)(3), that the submission date of patent information provided by an NDA holder after approval of an application is the earlier of the date on which Form FDA 3542 is date-stamped by the OGD Document Room or officially received electronically by FDA through the Electronic Submissions Gateway (i.e., at the completion of electronic transmission). Our current regulations state that the information shall be considered submitted to FDA on the date it is received by the Central Document Room. We note that patent information sent to another location at FDA is not considered received by FDA for purposes of § 314.53(d)(3) on timely filing and a 505(b)(2) or ANDA applicant's patent certification obligations pursuant to § 314.50(i)(4) and (i)(6) or § 314.94(a)(12)(vi) and (a)(12)(viii), respectively, unless it is sent to the official repository identified in the regulation.

These proposed revisions are intended to remove any ambiguity about the date of submission in light of the implications of untimely filing of patent information on the patent certification obligations of 505(b)(2) applicants and ANDA applicants that rely upon the listed drug (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). In this regard, we note that the patent certification obligations of a 505(b)(2) or ANDA applicant arise upon the receipt by the official repository at FDA of the NDA holder's submission of patent information for a listed drug rather than the timing of publication of the patent information in the Orange Book (see section 505(b)(2)(A) and (j)(2)(A)(vii) of the FD&C Act; see also Teva Pharms., USA, Inc. v. Leavitt, 548 F.3d 103, at 108 (D.C. Cir. 2008) (noting that FDA "has consistently required ANDA applicants to certify to patents recently submitted to FDA, even if FDA had not yet published the patent in any version of the Orange Book"))).

However, for purposes of eligibility for 180-day exclusivity, an ANDA applicant is not permitted to submit a paragraph IV certification to a patent (e.g., a recently issued patent that claims the RLD) before the first working day after the day the patent is listed in the Orange Book (see section II.D.1.b.ii and II.E.4).

In addition, proposed § 314.53(d)(5) would change the addressee to whom submission of Form FDA 3542 should be sent from the Central Document Room to the OGD Document Room or the Electronic Submissions Gateway, consistent with proposed § 314.53(d)(4) discussed in section II.B.2.c.

II.B.3. Public Disclosure of Patent Information (Proposed § 314.53(e))

We are proposing to delete the reference in § 314.53(e) to monthly supplements to the Orange Book because the Agency no longer arranges for publication of monthly printed supplements to the Orange Book. Patent information listed in the Orange Book, which may be

accessed from the Agency's Web site, has been updated on a daily basis for several years. This correction to § 314.53(e) is consistent with our proposed revision of the definition of "the list" in § 314.3(b) to mean the list of approved drug products published in FDA's current "Approved Drug Products With Therapeutic Equivalence Evaluations" available electronically on FDA's Web site at <http://www.fda.gov/cder>.

Section 314.53(e) provides that copies of the patent information submitted on Form FDA 3542 may be requested from FDA's Freedom of Information Staff. We are proposing to revise § 314.53(e) to replace the reference to a request for copies of the "file" to copies of the "submitted patent information." This revision is proposed for clarity and does not represent a substantive change. We note, for example, that some prospective 505(b)(2) or ANDA applicants have requested copies of the patent information submitted on Form FDA 3542 for patents listed for a listed drug in the Orange Book to determine the scope of the labeling identified by the NDA holder as relating to the use claimed by the patent. Copies of Form FDA 3542 also have been requested to obtain address information for the agent or representative authorized to receive notice of patent certification if the patent owner or NDA holder does not reside or have a place of business in the United States. We anticipate additional requests for the information submitted on Form FDA 3542 and may elect to proactively post on FDA's Web site a copy of Form FDA 3542 for patents listed in the Orange Book in advance of a request under the Freedom of Information Act (see Presidential Documents, Memorandum for the Heads of Executive Departments and Agencies on Transparency and Open Government (January 21, 2009) (74 FR 4685, January 26, 2009); see also Office of the Attorney General, Memorandum for the Heads of Executive Departments and Agencies on The Freedom of Information Act (March 19, 2009), available at <http://www.usdoj.gov/ag/foia-memo-march2009.pdf>).

II.B.4. Correction or Change of Patent Information (Proposed § 314.53(f))

We are proposing to revise § 314.53(f) to differentiate the procedure for correction or change of patent information by the NDA holder (proposed § 314.53(f)(2)) from the procedure for requests by persons other than the NDA holder. Proposed § 314.53(f) also would address certain issues that have arisen regarding method-of-use patents and enhance FDA's response to challenges to the accuracy or relevance of submissions of this patent information to the Agency. We are proposing to redesignate the current text of § 314.53(f) as § 314.53(f)(1). We are proposing to add new § 314.53(f)(2) to implement section 505(j)(5)(D)(i)(I)(bb)(CC) of the FD&C Act, as added by the MMA, and to make other changes for the efficient enforcement of the FD&C Act.

Table 4 summarizes the proposed changes related to correction or change of patent information:

Table 4.--Highlights of Proposed Changes Regarding Correction or Change of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Correction of patent information errors (§ 314.53(f))</u></p> <ul style="list-style-type: none"> If any person disputes the accuracy or relevance of patent information submitted to FDA under § 314.53 and published by FDA in the list, that person must first notify FDA (OGD Document Room, Attn: Orange Book Staff) in writing stating the grounds for disagreement. FDA then will request that the NDA holder confirm the correctness of the patent information. Unless the NDA holder withdraws or amends its patent information in response to FDA's request to confirm the correctness of the patent information, FDA will not change the patent information in the list. 	<p><u>Correction or change of patent information-- Requests by persons other than the NDA holder (§ 314.53(f)(1))</u></p> <ul style="list-style-type: none"> If any person disputes the accuracy or relevance of patent information submitted to FDA under § 314.53 and published by FDA in the list, that person must first notify FDA (OGD Document Room, Attn: Orange Book Staff) in a written or electronic communication titled "314.53(f) Patent Listing Dispute" that states the grounds for disagreement. FDA then will request that the NDA holder confirm the correctness of the patent information within 30 days. For listed patents that claim an approved method of using the drug product, FDA will request that the NDA holder confirm the correctness of the "Use Code" in the Orange Book, and provide information on the specific approved use claimed by the patent that enables FDA to make a determination in accordance with section 505(b)(2)(B) or (j)(2)(C)(viii) of the FD&C Act. Unless the NDA holder withdraws or amends its patent information in response to FDA's request to confirm the correctness of the patent information, FDA will not change the patent information in the list. --If there is insufficient information to make a determination in accordance with section 505(b)(2)(B) or (j)(2)(C)(viii) of the FD&C Act and the NDA holder has confirmed the correctness of its description of the specific approved use claimed by the patent, the Agency will review the proposed labeling for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.

Table 4.--Highlights of Proposed Changes Regarding Correction or Change of Patent Information¹

Current Regulations	Proposed Revisions to Regulations
	<p data-bbox="776 260 1256 317"><u>Correction or change of patent information-- Requests by the NDA holder (§ 314.53(f)(2))</u></p> <ul data-bbox="776 323 1333 1451" style="list-style-type: none"> <li data-bbox="776 323 1333 506">• If the NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, the NDA holder must promptly notify FDA to withdraw the patent information and request that the patent information be removed from the list. <li data-bbox="776 533 1333 810">• If the NDA holder is required by court order to amend patent information or withdraw a patent from the list, it must submit a copy of the order to FDA (OGD Document Room, Attn: Orange Book Staff) within 14 days of order entry. FDA will remove a patent from the list if there is no first applicant eligible for 180-day exclusivity or upon the expiration of the 180-day period. <li data-bbox="776 842 1333 1024">• If the term of a listed patent is extended under 35 U.S.C. 156(e), the NDA holder must submit on Form FDA 3542 a correction to the patent expiration date within 30 days of receipt of a certificate of extension or documentation of an extension of the patent term. <li data-bbox="776 1056 1333 1209">• Corrections or changes to previously submitted patent information, other than withdrawal of a patent and requests to remove a patent from the list (delisting requests), must be submitted on Form FDA 3542 or 3542a, as appropriate. <li data-bbox="776 1241 1333 1451">• Withdrawal of a patent and delisting requests must be submitted as described in § 314.53(d)(4), except it need not be submitted on Form FDA 3542. The patent withdrawal and delisting request must contain the NDA number, each product to which the request applies, and the patent number.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.B.4.a. Requests by persons other than the NDA holder--patents that claim an approved method of using the drug product (proposed § 314.53(f)(1)). To efficiently implement the statutory provisions in section 505(b)(2)(B) and (j)(2)(C)(viii) of the FD&C Act, we are proposing to enhance the mechanism for challenging the accuracy or relevance of information

with respect to method-of-use patents submitted to the Agency under § 314.53 and listed in the Orange Book.

In the preamble to the June 2003 final rule on patent submission and listing requirements, we discussed our longstanding position, codified in § 314.53(b) and (c)(2), that “only method-of-use patents that claim a use of the drug product in the pending or approved application must be submitted” (68 FR 36676 at 36681). The June 2003 final rule further explained: “The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use. This information will expedite our review of ANDA and 505(b)(2) applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can ‘carve out’ the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book” (68 FR 36676 at 36682).

An NDA holder or patent owner must provide adequate information in its submission of patent information to enable potential 505(b)(2) and ANDA applicants to avail themselves of the statutory provision that permits a 505(b)(2) or ANDA applicant to not certify to a patent by stating that it is not seeking approval for the method of use claimed by the listed patent (see section 505(b)(2)(B) and (j)(2)(C)(viii) of the FD&C Act, respectively) and carving out from product labeling the corresponding use information. Our July 2007 revision of Forms FDA 3542a and 3542 clarifies, in its instructions, that “[t]he use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent

claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval” (Form FDA 3542, section 4.2b).

Section 314.53(f) currently provides that, upon notification of the grounds for a disagreement with the accuracy or relevance of the patent submission, FDA will request that the NDA holder confirm the correctness of the patent information or omission of patent information. Proposed § 314.53(f)(1) would establish a 30-day timeframe in which the NDA holder is required to respond to FDA’s request in order to facilitate timely resolution of the patent listing dispute.

Proposed § 314.53(f)(1) also would further specify that, in response to notification of a patent listing dispute for a listed patent that claims an approved method of using the drug product, FDA will request that the NDA holder confirm the correctness of its description of the approved indication or method of use that has been included as the “use code” in the Orange Book, and provide information on the specific approved use claimed by the patent that enables the Agency to make a determination in accordance with section 505(b)(2)(B) or (j)(2)(C)(viii) of the FD&C Act. If the patent has been listed and the NDA holder confirms the accuracy of the patent information, fails to timely respond to FDA’s request under § 314.53(f), or submits a revision to the use code that does not provide adequate clarity for FDA to determine whether the scope of the proposed labeling carve-out would be appropriate based on the NDA holder’s use code and approved labeling, FDA is proposing to review a proposed labeling carve-out(s) for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant’s interpretation of the scope of the patent. In determining whether a proposed omission of use information from labeling is appropriate, the Agency will consider the use code and labeling information submitted by the NDA holder on Form FDA 3542, the history of labeling changes

related to approval of an indication(s) for the drug product, the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent, the need for consistent labeling among products approved under section 505(j) of the FD&C Act, and the requirements of §§ 314.94(a)(8)(iv) and 314.127(a)(7), as appropriate.

The following hypothetical example illustrates our approach under proposed § 314.53(f)(1) to determining whether an ANDA applicant's proposed labeling carve-out would be appropriate: The NDA holder submits Form FDA 3542 to the Office of Generic Drugs, Document Room, Attention: Orange Book Staff, within 30 days after issuance of the '321 patent claiming a method of using the drug product Gaindrolone. The NDA holder provided the use code "to promote weight gain after weight loss in certain types of patients" for each patent that it submitted for listing in the Orange Book, but did not specifically identify the approved use(s) (e.g., patient population(s)) claimed by the patent. In section 4.2a of Form FDA 3542, the NDA holder further identified the patented method of use claimed in patent claims 8, 9, and 10 of the '321 patent with specific reference to the following sections of the approved labeling for the drug product: Indications and Usage ("indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma") and Dosage and Administration. Applicant A submits an ANDA that cites Gaindrolone as the basis for ANDA submission and contains a 505(j)(2)(A)(viii) statement with respect to the '321 patent. Applicant A also notifies the Agency in a written communication titled "314.53(f) Patent Listing Dispute" that the use code listed in the Orange Book for the '321 patent is overbroad as Applicant A interprets the scope of the '321 patent to be limited to "adjunctive therapy to promote weight gain after weight loss following chronic infections." Applicant A contends that other approved patient populations are not within the scope of the '321 patent. FDA subsequently provides the

NDA holder with the Applicant A's basis for disagreement with the accuracy of the listed patent information and requests that the NDA holder confirm the correctness of the description of the specific approved use claimed by the patent or revise the description within 30 days. The NDA holder confirms the use code "to promote weight gain after weight loss in certain types of patients" and thus does not provide adequate clarity for the Agency to make a determination in accordance with section 505(j)(2)(A)(viii) of the FD&C Act on whether Applicant A could carve out the patented use in "certain types of patients" and seek approval for the remaining uses. Accordingly, FDA reviews the proposed ANDA labeling with deference to Applicant A's interpretation of the scope of the patent and approves the ANDA for "adjunctive therapy to promote weight gain after weight loss following extensive surgery or severe trauma." As noted in the June 2003 final rule, "the claim-by-claim listing of method-of-use patents will permit ANDA and 505(b)(2) applicants to assess whether they are seeking approval for a use claimed in the listed patent, and thus determine whether to submit a patent certification or a section viii statement. Additionally, we [FDA] can verify that the certification or statement is correct, and that only the appropriate methods of use are included in the proposed labeling for the ANDA or 505(b)(2) drug product" (68 FR 36676 at 36685). Applicant A has a strong incentive to interpret the scope of the patent correctly to avoid being subject to patent infringement litigation following ANDA approval and potentially enjoined from marketing its product. The use code submitted by the NDA holder remains listed in the Orange Book (compare June 2003 final rule (68 FR 36676 at 36683) ("[u]se codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling").

In the same example above, we note that if the NDA holder had responded to FDA's request by revising the description of the specific approved use claimed by the patent in a manner that provided sufficient information for the Agency to make a determination in accordance with section 505(j)(2)(A)(viii) of the FD&C Act on whether Applicant A could carve out the patented use, FDA would have no occasion to review the proposed ANDA labeling with deference to Applicant A's interpretation of the scope of the patent. For example, if the NDA holder submitted a revised Form 3542 that provided a revised use code (hypothetically "to promote weight gain after weight loss following chronic infections or severe trauma") and specifically referred to the corresponding portion of the approved labeling, there would be sufficient information for the Agency to make a determination in accordance with section 505(j)(2)(A)(viii) of the FD&C Act. Accordingly, there would be no ambiguity that would warrant review of the proposed ANDA labeling with deference to Applicant A's interpretation of the scope of the patent, even if Applicant A's interpretation differed from that of the NDA holder.

As previously discussed in the June 2003 final rule, we reiterate that the Agency's role in patent listing is ministerial and does not involve substantive review of patents (see 68 FR 36676 at 36683). Rather, our proposed revisions to the regulations in 314.53(f) are intended to provide the Agency with the information necessary to implement section 505(b)(2)(B) and (j)(2)(C)(viii) of the FD&C Act. FDA believes that enhancing the mechanism for challenging overbroad use codes listed in the Orange Book may cause NDA holders to be more circumspect in their original submission of patent information to FDA. Accordingly, we expect that there will rarely be a need for the Agency to review the proposed labeling for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.

However, we invite comment on this proposed approach to enhancing FDA's response to challenges to the accuracy or relevance of submissions of patent information to the Agency, while maintaining the Agency's ministerial role in patent listing.

II.B.4.b. Requests by NDA holder to remove patent information from the list (proposed § 314.53(f)(2)).

II.B.4.b.i. Patents or patent claims that no longer meet the statutory requirements for listing. Section 1102(a)(2) of the MMA amends section 505(j)(5)(D)(i)(I) of the FD&C Act to define certain events that constitute forfeiture of 180-day exclusivity. As noted in section I, we are implementing the 180-day exclusivity provisions of the MMA directly from the statute and will determine if additional rulemaking is necessary in the future. Where a novel issue of interpretation is raised by a particular factual scenario regarding forfeiture of 180-day exclusivity, we may open a public docket or otherwise seek comment from affected parties in advance of taking action (see section I.D). However, we are proposing at this time to add § 314.53(f)(2) regarding requests by an NDA holder to remove patent information from the list to implement section 505(j)(5)(D)(i)(I)(bb)(CC) of the FD&C Act (forfeiture of 180-day exclusivity due to failure to market where the patent or patent information that qualified the first applicant for 180-day exclusivity is withdrawn by the NDA holder), and to clarify our current practice with respect to withdrawal of a patent or patent information by an NDA holder.

Under proposed § 314.53(f)(2), if the NDA holder determines that a patent or patent claim (e.g., a method-of-use claim) no longer meets the statutory requirements for listing, the NDA holder is required to promptly notify FDA to withdraw the patent or patent information and request that the patent or patent information be removed from the list. Circumstances under which a patent or patent claim no longer meets the statutory requirements for listing include, but

are not limited to, a judicial finding of invalidity or unenforceability for a listed patent, from which no appeal has been or can be taken, or a court order to amend patent information or withdraw a patent from the list. We note that an NDA applicant that determined that a patent or patent claim submitted on Form FDA 3542a no longer met the statutory requirements for listing prior to NDA approval would “withdraw” the patent or patent claim by not including the patent or patent claim in its submission of Form FDA 3542 upon approval of the NDA or NDA supplement. There is no need to submit a request to remove the patent or patent claim from the list because such patent information is listed in the Orange Book only upon approval of the NDA or NDA supplement.

The FD&C Act does not provide an independent cause of action for a 505(b)(2) or ANDA applicant seeking an order requiring an NDA holder to correct or delete patent information listed in the Orange Book (see section 505(c)(3)(D)(ii)(II) and (j)(5)(C)(ii)(II) of the FD&C Act; see also Mylan Pharmaceuticals, Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001) (holding that the pre-MMA statutory scheme did not recognize a cause of action for delisting a patent from the Orange Book, and that “such an action would be a private right of action barred by the [act]”). If a 505(b)(2) or ANDA applicant successfully asserts a counterclaim to a patent infringement action to obtain an order requiring the NDA holder to amend or withdraw patent information from the list (see section 505(c)(3)(D)(ii)(I) and (j)(5)(C)(ii)(I) of the FD&C Act), the NDA holder must withdraw the patent or patent information and request that the patent or patent information be removed from the list. The Agency will not remove the patent or patent information in response to a request, accompanied by a copy of the court order, from the 505(b)(2) or ANDA applicant or on its own. We are proposing to require an NDA holder to submit a copy of a court order requiring amendment or withdrawal of patent information to the

Orange Book Staff through the Office of Generic Drugs Document Room within 14 calendar days of the date on which the order was entered. By providing a 14-day timeframe within which an NDA holder must notify FDA of this type of court order, the proposed regulation would facilitate the NDA holder's compliance with obligations under the FD&C Act and applicable regulations and ensure that pending 505(b)(2) applications or ANDAs that have provided a patent certification to the amended or withdrawn patent are not inappropriately delayed if they are otherwise eligible for approval. The Orange Book Staff subsequently will forward a copy of the court order to the NDA through the CDER Central Document Room.

We recognize that for patents that meet the statutory criteria for listing in the Orange Book, fewer than all of the patent claims may be the subject of litigation against a particular 505(b)(2) or ANDA applicant. In such a case, a judicial finding of invalidity for certain patent claims and withdrawal of that patent information by submission of an amended Form FDA 3542 may not necessarily be reflected in the Orange Book (unless, for example, all drug product claims were invalidated and only a method-of-use claim remained). Accordingly, it would be prudent for current and prospective 505(b)(2) and ANDA applicants to be aware of relevant court decisions in patent litigation (see also the 1994 final rule (59 FR 50338 at 50346)(noting the prudence of conducting patent searches to identify patents that may be ineligible for listing in the Orange Book but that may be infringed by a proposed product)).

Consistent with our current practice, proposed § 314.53(f)(2) states that we will remove a patent from the Orange Book when the NDA holder has informed us that the patent no longer meets the statutory requirements for listing if there is no first applicant eligible for 180-day exclusivity or upon the expiration of the 180-day exclusivity period of a first applicant.

Proposed § 314.53(f)(2) also applies to amendment of the patent information to remove a claim (drug substance, drug product, or method of use) from the list. For example, if a patent is listed in the Orange Book as claiming the drug product and a method of use, and an NDA holder withdrew only the drug product claim and requested that the drug product claim be removed from the list, we would remove the drug product claim from the Orange Book if there is no first applicant eligible for 180-day exclusivity or upon the expiration of the 180-day exclusivity period of a first applicant. This provision is intended to address scenarios in which an ANDA applicant has submitted a paragraph IV certification with respect to the drug substance or drug product claim and a 505(j)(2)(C)(viii) statement with respect to a method-of-use claim for a single patent.

When an NDA holder has withdrawn a patent and submitted to FDA a request to remove the patent from the Orange Book, we currently identify this request in a separate column in the Orange Book titled “Delist Requested.” If an NDA holder withdraws a patent claim (e.g., a method-of-use claim in a patent that also claims the drug product) and submits to FDA a request to remove the patent claim from the Orange Book, we intend to identify this request with a symbol (e.g., an asterisk) in the column for that claim. These notations signal that the patent or patent claim remains listed in the Orange Book only to preserve a first applicant’s eligibility for 180-day exclusivity for their pending ANDA or during the period of 180-day exclusivity after approval of the first applicant’s ANDA. While the patent or patent claims remain listed in the Orange Book, subsequent ANDA applicants must submit or maintain an appropriate patent certification or statement with respect to the patent or patent claims for which the delisting request has been submitted. This requirement is consistent with preservation of a first applicant’s eligibility for 180-day exclusivity because the 180-day exclusivity period bars

approval of subsequent ANDAs for the same drug product that also contain a paragraph IV certification to the patent (see section 505(j)(5)(B)(iv)(I) of the FD&C Act). However, a 505(b)(2) applicant is not required to certify or maintain a previous certification to the patent for which a request to remove the patent from the list has been submitted, because such a patent remains listed in the Orange Book only for purposes of preserving a first ANDA applicant's eligibility for 180-day exclusivity.

An applicant can determine that a patent or patent claim has been removed from the Orange Book if it no longer appears in the Orange Book patent listings for the drug product at issue. In addition, FDA maintains a separate Web page linked from the "search by patent" option on the Orange Book Web page that identifies patents that have been recently delisted (currently located at <http://www.accessdata.fda.gov/scripts/cder/ob/docs/delist.cfm>).

II.B.4.b.ii. Patent term restoration. Proposed § 314.53(f)(2)(ii) directs NDA holders to submit a correction to the expiration date of their listed patent if the term of the patent is extended under the patent term restoration provisions of 35 U.S.C. 156, and sets a timeframe for compliance. With respect to patents eligible for listing in the Orange Book, the Hatch-Waxman Amendments generally provide that the terms of certain patents may be extended for a period of up to 5 years if the patent claims a product or method of using a product that has been subject to a defined regulatory review period before commercial marketing or use (see 35 U.S.C. 156(a)). We are proposing to require the NDA holder to submit the correction to the patent expiration date on Form FDA 3542 within 30 calendar days of receipt of a certificate of extension as described in 35 U.S.C 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2). The 30-day timeframe within which an NDA holder must notify FDA of the patent term extension is consistent with the statutory timeframe set forth in

section 505(c)(2) of the FD&C Act for filing with FDA the patent number and patent expiration date of any patent that claims the drug or method of using the drug and is issued after NDA approval. Although extension of the patent term of a previously issued patent is not explicitly within the scope of section 505(c)(2) of the FD&C Act, the proposed 30-day timeframe for submission of a correction of the patent expiration date is consistent with the objective of ensuring that prospective 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug.

II.B.4.b.iii. Submissions to FDA. Proposed § 314.53(f)(2)(iii) would require that corrections or changes to previously submitted patent information (other than withdrawal of a patent or requests to remove a patent from the list) must be submitted on Form FDA 3542a or 3542, as appropriate. This proposed requirement is intended to facilitate listing of patent information in the Orange Book and ensure that patent information is accompanied by the patent declaration verification required by § 314.53(c)(2)(i)(Q) and (c)(2)(ii)(R) and set forth in the certification requirements of Form FDA 3542a or 3542, respectively. We note that we will not accept corrections or changes that are not submitted on the appropriate forms. However, an NDA holder may elect to submit a cover letter highlighting the corrections or changes made in the accompanying Form FDA 3542. An NDA holder's withdrawal of fewer than all of a previously submitted patent's claims (e.g., withdrawal of the method of use claim(s) for a patent that also claims the drug product) would be considered a correction or change to patent information for purposes of proposed § 314.53(f)(2)(iii) because the patent would remain listed in the Orange Book.

However, proposed § 314.53(f)(2)(iv) clarifies that an NDA holder's withdrawal of a patent and request to remove a patent from the Orange Book is not required to be submitted on

Form FDA 3542a (with respect to pre-approval withdrawal of a patent) or FDA Form FDA 3542.

The withdrawal of a patent must be submitted as an amendment to the NDA if the application has not been approved. After NDA approval, the withdrawal of a patent must be submitted to the Orange Book Staff through the OGD Document Room and must specify the patent number, the application number, and each product(s) approved in the application to which the request applies. The Orange Book Staff subsequently will forward a copy of the patent withdrawal to the NDA through the CDER Central Document Room.

II.C. Patent Certification (Proposed §§ 314.50(i) and 314.94(a)(12))

II.C.1. Method-of-Use Patents (Proposed §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii))

We are proposing to revise §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii) to clarify that a 505(b)(2) or ANDA applicant that is not seeking approval for any indications or other conditions of use that are covered by a method-of-use patent for the listed drug(s) relied upon or RLD, respectively, and has omitted corresponding labeling from its proposed product may submit a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii), respectively, instead of a patent certification with respect to any method-of-use claims. The proposed addition of the phrase “or other conditions of use” to §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii) reflects that a method-of-use patent that claims a use other than an indication may be submitted for listing in the Orange Book and may be the subject of a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) with an accompanying labeling carve-out. This proposed revision is intended to conform with current Agency practice.

II.C.2. Method-of-Manufacturing Patents (Proposed Deletion of §§ 314.50(i)(2) and 314.94(a)(12)(iv))

The current regulations in §§ 314.50(i)(2) and 314.94(a)(12)(iv) state that a 505(b)(2) or ANDA applicant, respectively, is not required to make a patent certification with respect to any patent that claims only a method of manufacturing the drug product (method-of-manufacturing patent). This has been incorrectly interpreted by certain applicants to mean that a manufacturer could elect to submit such a patent for listing. In 2003, § 314.53(b) was amended to state, among other things, that process patents (i.e., method-of-manufacturing patents) must not be submitted to FDA (68 FR 36676 at 36679). Therefore, we are proposing that current §§ 314.50(i)(2) and 314.94(a)(12)(iv) be removed (and reserved) to ensure consistency and clarity in our regulations.

II.C.3. Licensing Agreement (Proposed § 314.50(i)(3))

We are proposing to revise § 314.50(i)(3) regarding licensing agreements to remove the references to an “immediate effective date” and clarify that the patent owner with whom the applicant has a licensing agreement may consent to approval of the 505(b)(2) application (if otherwise justified) as of a specific date. These proposed revisions reflect that there may be barriers to approval other than the patent that is the subject of the licensing agreement. In addition, the proposed revision acknowledges that a patent owner may consent to approval as of a specific date.

This proposed revision does not alter the current requirements for a 505(b)(2) (or ANDA) applicant that submits a paragraph IV certification to a patent that claims the listed drug relied upon and for which the applicant has a licensing agreement with the patent owner (see proposed §§ 314.50(i)(3) and 314.94(a)(12)(v)). A 505(b)(2) or ANDA applicant must comply with the statutory requirements for sending notice of paragraph IV certification under section 505(b)(3)

and (j)(2)(B) of the FD&C Act, respectively, with respect to each listed patent for which it has submitted a paragraph IV certification notwithstanding the applicant's statement that it has been granted a patent license.

II.D. Notice of Paragraph IV Certification (Proposed §§ 314.52 and 314.95)

II.D.1. Timing of Notice

A 505(b)(2) or ANDA applicant submitting a paragraph IV certification is required to give notice of the patent challenge to the holder of the NDA for the listed drug(s) relied upon or RLD, respectively, and each owner of the patent that is the subject of the certification within a specified timeframe (see section 505(b)(3) and (j)(2)(B) of the FD&C Act). We are proposing to revise our regulations to clearly delineate the two limitations on the timeframe within which notice can be provided to the NDA holder and each patent owner of a paragraph IV certification to a listed patent: (1) The date before which notice may not be given and (2) the date by which notice must be given. The MMA amended the FD&C Act to establish the date by which notice of a paragraph IV certification must be given to the NDA holder and each patent owner. Table 5 summarizes the proposed changes related to the timing of providing notice of a paragraph IV certification.

Table 5.--Highlights of Proposed Changes Regarding Timing of Notice of Paragraph IV Certification¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Sending the notice (§§ 314.52(b) and 314.95(b))</u></p> <ul style="list-style-type: none"> • 505(b)(2) applicant must send notice required by § 314.52(a) when it receives from FDA an acknowledgment letter stating that its 505(b)(2) application has been filed. • ANDA applicant must send notice required by § 314.95(a), when it receives from FDA an acknowledgment letter stating that its ANDA is sufficiently complete to permit a substantive review. 	<p><u>Sending the notice (§§ 314.52(b)(1) and (b)(2) and 314.95(b)(1) and (b)(2))</u></p> <ul style="list-style-type: none"> • Except as provided in § 314.52(d), a 505(b)(2) applicant must send notice required by § 314.52(a) on or after the date it receives from FDA a paragraph IV acknowledgment letter, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. • Any required notice is invalid if it is sent before the 505(b)(2) applicant's receipt of a paragraph IV acknowledgment letter. The applicant will not have complied with § 314.52(b) until it sends valid notice. • Except as provided in § 314.95(d), an ANDA applicant must send notice required by § 314.95(a) on or after the date it receives from FDA an acknowledgment letter or a paragraph IV acknowledgment letter, but not later than 20 days after the date of the postmark on the acknowledgment letter or paragraph IV acknowledgment letter. • Any required notice is invalid if it is sent before the ANDA applicant's receipt of an acknowledgment letter or a paragraph IV acknowledgment letter, or before the first working day after the day the patent is published in the list. The applicant will not have complied with § 314.95(b) until it sends valid notice. • The 20-day clock begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.
<p><u>Sending the notice (§§ 314.52(b) and 314.95(b))</u></p> <ul style="list-style-type: none"> • At the same time, the 505(b)(2) or ANDA applicant must amend its application to include a statement certifying that notice of paragraph IV certification has been provided to each person identified under § 314.52(a) or § 314.95(a), respectively, and that notice met the content requirement under § 314.52(c) or § 314.95(c), respectively. 	<p><u>Sending the notice (§§ 314.52(b)(3) and 314.95(b)(3))</u></p> <ul style="list-style-type: none"> • At the same time the 505(b)(2) or ANDA applicant sends the notice required by § 314.52(a) or § 314.95(a), respectively, it must submit an amendment to its 505(b)(2) application that includes a statement certifying that the notice of paragraph IV certification has been provided to each person under § 314.52(a) or § 314.95(a), respectively, and that notice met the content requirement under § 314.52(c) or § 314.95(c), respectively.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.D.1.a. Date before which notice may not be given. We are proposing to clarify the text of our regulations to reflect our longstanding practice that notice of a paragraph IV certification may not be sent by a 505(b)(2) or ANDA applicant unless and until we have notified the applicant that its application has been filed or received, as appropriate, in an acknowledgment letter or a paragraph IV acknowledgment letter (see proposed §§ 314.52(b)(1) and 314.95(b)(1)).

Sections 314.52(b) and 314.95(b) currently require that a 505(b)(2) and ANDA applicant, respectively, send notice of a paragraph IV certification when it receives from FDA an acknowledgment letter stating that the application is sufficiently complete to permit a substantive review. An NDA, including a 505(b)(2) application, is deemed sufficiently complete to permit a substantive review if it is filed by the 60th day after submission (see § 314.101(a)(1) and proposed § 314.101(a)(2)). An ANDA is received when FDA has made a threshold determination that the ANDA is substantially complete and has sent the ANDA applicant an acknowledgment letter or paragraph IV acknowledgment letter (see § 314.101(b)). We previously have explained that notice of a paragraph IV certification is to be sent only after the 505(b)(2) or ANDA applicant has received acknowledgment from FDA that its application has been determined to be acceptable for review because such notice subjects the 505(b)(2) or ANDA applicant to the risk that it will be sued for patent infringement (see “Abbreviated New Drug Application Regulations”; proposed rule (54 FR 28872; July 10, 1989) (1989 proposed rule); see also 35 U.S.C. 271(e)(2)). The receipt of notice of a paragraph IV certification by a patent owner or the NDA holder (or their representatives) begins a 45-day period within which the NDA holder or patent owner must initiate a patent infringement action against the 505(b)(2) or ANDA applicant in order to obtain, in certain cases, a statutory 30-month stay of approval of

the application while the patent infringement litigation is pending (section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

The FD&C Act requires that a notice of paragraph IV certification must state that the 505(b)(2) application or ANDA containing the certification “has been submitted” (see section 505(b)(3)(D)(i) and (j)(2)(B)(iv)(I) of the FD&C Act). As we noted in the preamble to the 1989 proposal to implement the Hatch-Waxman Amendments, however, “[t]he statute and legislative history of Title I [of the Hatch-Waxman Amendments] demonstrate that Congress did not intend incomplete application submissions to trigger legal action by a patent owner or approved application holder” (1989 proposed rule, 54 FR 28872 at 28887). By requiring that a 505(b)(2) application has been filed or an ANDA has been received before notice of a paragraph IV certification can be given, we ensure that the NDA holder and patent owner do not needlessly expend resources to initiate litigation with respect to an application that is incomplete and therefore may not be reviewed by the Agency (see 1989 proposed rule, 54 FR 28872 at 28887 and 1994 final rule, 59 FR 50338 at 50349-50350). Accordingly, our current regulations require that a 505(b)(2) or ANDA applicant’s notice of a paragraph IV certification must include a statement that FDA has filed the NDA (in the case of a 505(b)(2) application) or has received the ANDA (see §§ 314.52(c)(1) and 314.95(c)(1)).

Despite the language in our existing regulations and the preamble to the 1989 proposed rule, we have continued to receive inquiries from the public regarding whether notice of paragraph IV certification may be sent before the filing of a 505(b)(2) application or receipt of an ANDA. Some have expressed uncertainty after enactment of the MMA because the FD&C Act requires that notice be sent “not later than 20 days after the date of the postmark on the notice with which [FDA] informs the applicant” that its 505(b)(2) application or ANDA has been filed,

without explicitly establishing a date earlier than which notice may not be provided (see section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act).

We are proposing to amend §§ 314.52(b) and 314.95(b) by revising and redesignating the current text as paragraphs (b)(1) and (b)(3) and adding a new paragraph (b)(2). Proposed § § 314.52(b)(2) and 314.95(b)(2) state that any notice sent before the receipt of an FDA acknowledgment letter or paragraph IV acknowledgment letter is invalid (and thus does not trigger either the 45-day period in which the NDA holder and each patent owner may initiate a patent infringement action and obtain a 30-month stay or the beginning of any related 30-month period) and will not be considered to comply with the FD&C Act's notice requirement until valid notice is sent. We also are proposing to revise § 314.95(b)(2) to state that any notice sent before the first working day after the day the patent is published in the Orange Book (the list) is invalid and will not be considered to comply with the FD&C Act's notice requirement (see discussion in section II.D.1.b.ii).

An applicant that prematurely sends notice of a paragraph IV certification must resend notice within the required timeframe in order to satisfy the notice requirement of the FD&C Act and, in the case of a first applicant, qualify for 180-day exclusivity. To help ensure that notices of paragraph IV certifications are not sent prematurely, we also are proposing to amend § § 314.52(c)(3) and 314.95(c)(3) to require that each 505(b)(2) or ANDA applicant include, in any notice of paragraph IV certification related to its application, a statement that it has received an acknowledgment letter or paragraph IV acknowledgment letter. We recognize that this proposed requirement may have the effect of delaying the provision of notice of paragraph IV certification by a 505(b)(2) applicant (but not an ANDA applicant) by approximately 2 weeks after the 505(b)(2) application is filed, because an NDA is considered filed 60 days after

submission, but our proposed definition of a “paragraph IV acknowledgment letter” for a 505(b)(2) application is the filing communication that is generally mailed by the 74th day after the date of submission of the 505(b)(2) application in accordance with the performance goal established under the current reauthorization of the prescription drug user fee program in FDASIA (see section II.D.3.b). We recognize that this would potentially delay the initiation of patent infringement litigation by an NDA holder or patent owner and any corresponding 30-month stay of approval of the 505(b)(2) application by approximately 2 weeks. We invite comment on this approach to premature notice of a paragraph IV certification for a 505(b)(2) application, especially with respect to notice sent after a 505(b)(2) application is filed (60th day after submission) and before a paragraph IV acknowledgment letter (generally sent by the 74th day after submission) is received.

There have been some instances in which an applicant seeks to submit an amendment containing a paragraph IV certification to its 505(b)(2) application or ANDA prior to filing or receipt of the application as described in § 314.101(a) and (b), respectively, and receipt of an acknowledgment letter or a paragraph IV acknowledgment letter. For example, an applicant may seek to amend its ANDA to add a new strength of the drug product (see § 314.95(d)(3)). We are proposing to revise §§ 314.52(d)(2) and 314.95(d)(2) to clarify that an applicant submitting an amendment containing a paragraph IV certification must comply with the timeframes set forth in §§ 314.52(b) and 314.95(b) and wait until it has received an acknowledgment letter or a paragraph IV acknowledgment letter before sending notice of its paragraph IV certification to the NDA holder and each patent owner. This approach ensures that a notice of paragraph IV certification is not sent before we have accepted for substantive review the underlying application to which the notice relates (i.e., before we have filed the 505(b)(2) application or

received the ANDA). As one Federal district court observed in upholding FDA's interpretation of the statute in this scenario, "[i]f an ANDA applicant could send Paragraph IV notice when amending an ANDA that has not yet been accepted as received, the applicant could accelerate the timing provisions and litigation process well beyond the framework that Congress intended" (SB Pharmco Puerto Rico, Inc. v. Mutual Pharmaceutical Co., 552 F. Supp. 2d 500, 510 (E.D. Pa.), appeal dismissed, 2008 U.S. App. LEXIS 27672 (Fed. Cir. 2008) (holding that notice of a paragraph IV certification sent concurrent with submission of an amendment to an ANDA that had not yet been accepted for filing "was not valid or timely" under section 505(j)(2)(B)(ii)(II) of the FD&C Act)).

Thus, if an ANDA applicant submits an amendment containing a paragraph IV certification before it has received an acknowledgment letter or a paragraph IV acknowledgment letter advising that the ANDA has been received for substantive review, the applicant is required to send notice of its paragraph IV certification within 20 days after the date of the postmark on the acknowledgment letter or paragraph IV acknowledgment letter, as applicable. It is important to note that the relevant date for purposes of determining first applicant eligibility for 180-day exclusivity based upon submission of a paragraph IV certification contained in an amendment is the date of submission of the amendment (i.e., the date on which the amendment was officially received (date-stamped) by the OGD Document Room) even though the acknowledgment letter or paragraph IV acknowledgment letter may state that the ANDA was received for substantive review on the date on which the original ANDA was submitted (i.e., the date on which the ANDA was officially received (date-stamped) by the OGD Document Room) or, in the case of an ANDA that OGD initially refused to receive under § 314.101(d) or (e), the date on which the deficiencies were resolved.

II.D.1.b. Date by which notice must be given. The MMA amended the FD&C Act to require that 505(b)(2) and ANDA applicants provide notice of a paragraph IV certification to the NDA holder and each patent owner in accordance with the following timeframes:

- If the paragraph IV certification is included in an original 505(b)(2) application or ANDA, or in an amendment to such application that is submitted before the applicant receives an acknowledgment letter or paragraph IV acknowledgment letter, not later than 20 days after the date of the postmark on the notice from FDA informing the applicant that its application has been filed or received (see section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act), or
- If the paragraph IV certification is included in any other amendment or in a supplement, at the time the applicant submits the amendment or supplement (see section 505(b)(3)(B)(ii) and 505(j)(2)(B)(ii)(II) of the FD&C Act).

II.D.1.b.i. Determining the timeframe for sending notice after receipt of an acknowledgment letter or a paragraph IV acknowledgment letter. We are proposing to revise §§ 314.52(b)(1) and 314.95(b)(1) to require that an applicant must send notice of a paragraph IV certification contained in a 505(b)(2) application or ANDA on or after the date on which it receives an acknowledgment letter or a paragraph IV acknowledgment letter, but not later than 20 days after the date of the “postmark” (see proposed definition below) on the acknowledgment letter or paragraph IV acknowledgment letter. As discussed in sections II.A.2.u and II.A.2.y, we are proposing a broader definition of the term “postmark” and, as applied to paragraph IV acknowledgment letters for 505(b)(2) applications, an alternate interpretation of the term “postmark” to reflect current OND practice regarding the mailing of filing communications. For purposes of proposed § 314.52(b) and (c) only, the “date of the postmark” on the paragraph IV

acknowledgment letter for a 505(b)(2) application is considered to be 4 calendar days after the date on which the filing communication is signed by the signatory authority (generally the Division Director or designee in OND) unless OND sends the filing communication to the applicant via electronic transmission. If OND sends the filing communication via electronic transmission, then our proposed definition of “postmark” in § 314.3(b) would apply. We recognize that issuance of the filing communication within 14 days after the 60-day filing date described in § 314.101(a)(1) and (a)(2) represents a performance goal under the current reauthorization of the prescription drug user fee program in FDASIA. Accordingly, an applicant that has submitted a 505(b)(2) application containing a paragraph IV certification and has received neither a refuse-to-file letter within 60 days nor a filing communication within 74 days after FDA receives the 505(b)(2) application should contact FDA to request issuance of the filing communication. We invite comment on whether an alternate approach should be taken. With reference to an acknowledgment letter or a paragraph IV acknowledgment letter for an ANDA, we recognize that there may be scenarios in which the postmark on the envelope containing an acknowledgment letter or a paragraph IV acknowledgment letter is illegible or inadvertently absent. We invite comment on the interpretation of the term “postmark” in the context of an acknowledgment letter or a paragraph IV acknowledgment letter for a 505(b)(2) application or an ANDA, and whether our regulations should be amended to define differently the specific date on which the 20-day notice period begins.

The MMA does not specify how the 20-day period for providing notice of a paragraph IV certification is to be calculated. We are proposing in §§ 314.52(b)(1) and 314.95(b)(1) to calculate this notice period in the same way that we calculate the 45-day period within which each patent owner and NDA holder may initiate a patent infringement action (which may, if

other applicable requirements are satisfied, trigger a 30-month stay of approval of a 505(b)(2) application or ANDA) following receipt of notice of a paragraph IV certification (see § 314.107(f)). Specifically, we propose that the first day of the 20-day period begin on the day after the date of the postmark on the acknowledgment letter or paragraph IV acknowledgment letter. The 20-day period is proposed to include all calendar days, except that if the 20th day falls on a Saturday, Sunday, or Federal holiday, the last day of the 20-day period will be considered to be the next day that is not a Saturday, Sunday, or Federal holiday. This approach reflects the most conservative interpretation of the statute and is the calculation method currently used by most ANDA applicants.

There will be no regulatory benefit or consequence for applicants based on when they provide notice of a paragraph IV certification contained in an original application, as long as notice is provided within the 20-day timeframe required by the MMA. An ANDA applicant that does not comply with the statutory timeframe in section 505(j)(2)(B)(ii)(I) and (j)(2)(B)(ii)(II) of the FD&C Act for providing notice of its paragraph IV certification will be subject to administrative consequences (see section II.D.5).

II.D.1.b.ii. Determining the timeframe for sending notice of a paragraph IV certification upon submission of an amendment or supplement. We are proposing to revise §§ 314.52(d) and 314.95(d) to implement section 505(b)(3)(B)(i), (b)(3)(B)(ii), (j)(2)(B)(ii)(I), and (j)(2)(B)(ii)(II) of the FD&C Act and for the efficient enforcement of the FD&C Act. Our proposed revisions clarify the applicable timeframe in which a 505(b)(2) or ANDA applicant must send notice of a paragraph IV certification submitted in an amendment or supplement to its 505(b)(2) application or ANDA, respectively. We are proposing to revise and redesignate the current text of §§ 314.52(d) and 314.95(d) as paragraph (d)(1) to accommodate the proposed inclusion of

additional paragraphs to §§ 314.52(d) and 314.95(d). Table 6 summarizes the proposed changes related to the timing of providing notice of paragraph IV certification(s) submitted in an amendment or supplement to a 505(b)(2) application or ANDA.

Table 6.--Highlights of Proposed Changes Regarding Timing of Notice of Paragraph IV Certification in an Amendment or Supplement¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Amendment to an application or an abbreviated application (§§ 314.52(d) and 314.95(d))</u></p> <ul style="list-style-type: none"> If an application or abbreviated application is amended to include the certification described in §§ 314.50(i) or 314.94(a)(12)(i)(A)(4), respectively, the applicant must send the notice required by §§ 314.52(a) or 314.95(a), respectively, at the same time the amendment is submitted to FDA. 	<p><u>Amendment or supplement to a 505(b)(2) application or an ANDA (§§ 314.52(d)(1) and 314.95(d)(1))</u></p> <p><u>After receipt of an acknowledgment letter or paragraph IV acknowledgment letter:</u></p> <ul style="list-style-type: none"> If an applicant submits an amendment or supplement to its 505(b)(2) application or ANDA that includes a paragraph IV certification, the applicant must send notice required by § 314.52(a) or § 314.95(a), respectively, at the same time the amendment is submitted to FDA. Notice of paragraph IV certification is required regardless of whether notice already has been provided for another paragraph IV certification contained in the application or in an amendment or supplement to the application.
	<p><u>Amendment to a 505(b)(2) application or an ANDA (§§ 314.52(d)(2) and 314.95(d)(2))</u></p> <p><u>Before receipt of an acknowledgement letter or paragraph IV acknowledgment letter:</u></p> <ul style="list-style-type: none"> If an applicant submits a paragraph IV certification in an amendment to a 505(b)(2) application or ANDA, the applicant must send notice required by § 314.52(a) or § 314.95(a), respectively, in accordance with the procedures in § 314.52(b) or § 314.95(b). If an ANDA applicant timely provides notice of paragraph IV certification in accordance with § 314.95(b), FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

Table 6.--Highlights of Proposed Changes Regarding Timing of Notice of Paragraph IV Certification in an Amendment or Supplement¹

Current Regulations	Proposed Revisions to Regulations
	<p data-bbox="776 285 1338 344"><u>Amendment to a 505(b)(2) application or an ANDA (§§ 314.52(d)(3) and 314.95(d)(3))</u></p> <ul data-bbox="776 344 1338 527" style="list-style-type: none"> <li data-bbox="776 344 1338 527">• An applicant that submits an amendment or supplement to its 505(b)(2) application or ANDA to seek approval of a new strength must provide notice of any paragraph IV certification in accordance with §§ 314.52(d)(1) and (d)(2) or §§ 314.95(d)(1) and (d)(2), as applicable.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

We are proposing to revise §§ 314.52(d) and 314.95(d) (redesignated as §§ 314.52(d)(1) and 314.95(d)(1), respectively) to require that an applicant send notice of a paragraph IV certification contained in an amendment to an application that has been received for substantive review or in a supplement to an approved application at the same time that the amendment or supplement is submitted to FDA. Our proposed revisions clarify the requirement in our current regulations for an applicant to send notice of a paragraph IV certification at the same time that the amendment is submitted to FDA by distinguishing between: (1) Amendments submitted after the application has been received for substantive review as indicated by the receipt of an acknowledgment letter (if, as to an ANDA, the original application did not contain a paragraph IV certification) or paragraph IV acknowledgment letter and (2) amendments submitted before an application has been received for substantive review (see proposed §§ 314.52(d)(2) and 314.95(d)(2) and section II.D.1.b.i.). The MMA amended the FD&C Act to require that notice of a paragraph IV certification contained in a supplement to an approved 505(b)(2) application or ANDA be sent at the same time that the supplement is submitted to FDA, and our proposed revision to §§ 314.52(d)(1) and 314.95(d)(1) incorporates this requirement (see section 505(b)(3)(B)(ii) and (j)(2)(B)(ii)(II) of the FD&C Act).

In proposed §§ 314.52(d)(1) and 314.95(d)(1), we reiterate the statutory requirement that notice of a paragraph IV certification in an amendment or supplement must be provided regardless of whether the applicant has already given notice with respect to another paragraph IV certification contained in the 505(b)(2) application or ANDA or in an amendment or supplement to the 505(b)(2) application or ANDA. The phrase “another paragraph IV certification” may refer to a previous paragraph IV certification to a different listed patent for the listed drug relied upon or RLD or, for certain amendments and supplements (see section II.F), a previous paragraph IV certification to the same listed patent. For example, if an ANDA applicant submitted a paragraph IV certification to the ’246 patent (a listed patent claiming the drug product for the listed drug relied upon) in its original application, and subsequently submitted an amendment to its pending ANDA to change the formulation, the ANDA applicant would be required to provide a new patent certification to the ’246 patent (see proposed § 314.96(d)(1) and section II.F.1). If this ANDA applicant submitted a paragraph IV certification to the ’246 patent in its amendment, the ANDA applicant would be required to send notice of its second paragraph IV certification to the ’246 patent to the NDA holder and each patent owner at the same time the amendment to the ANDA is submitted to FDA.

If an applicant submits an amendment containing a paragraph IV certification to its 505(b)(2) application or ANDA before the applicant has received an acknowledgment letter (if, as to an ANDA, the original application did not contain a paragraph IV certification) or a paragraph IV acknowledgment letter, proposed §§ 314.52(d)(2) and 314.95(d)(2) require that the applicant send notice of its paragraph IV certification in accordance with the procedures described in §§ 314.52(b) and 314.95(b), respectively. In this circumstance, the 505(b)(2) or ANDA applicant must send notice of the paragraph IV certification contained in its amendment

on or after the date it receives an acknowledgment letter or paragraph IV acknowledgment letter, but not later than 20 days after the date of the postmark on the letter. This requirement reflects our longstanding policy that notice of a paragraph IV certification may not be sent unless and until we have notified the applicant that its application has been filed or received, as appropriate (see section II.D.1.a).

It should be noted that a paragraph IV certification submitted in an amendment after the 505(b)(2) application or ANDA is submitted but before the applicant receives a paragraph IV acknowledgment letter is considered part of the original 505(b)(2) application or ANDA solely for the purpose of determining the appropriate timeframe for sending notice of paragraph IV certification. The availability of a 30-month stay for patent infringement litigation initiated within the statutory timeframe in response to a paragraph IV certification submitted in an amendment to a 505(b)(2) application or an ANDA continues to be determined by whether the patent at issue was filed with FDA before the date on which the original 505(b)(2) application or ANDA (excluding an amendment or supplement) was submitted (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act; see also proposed § 314.107(b)(2) and section II.M.2.b). For purposes of determining an ANDA applicant's eligibility for 180-day exclusivity and the date from which a first ANDA applicant's compliance with section 505(j)(5)(D)(i)(IV) of the FD&C Act is assessed, the date of the submission of the paragraph IV certification is the date on which the amendment was submitted. An amendment seeking approval for a different strength of a drug product thus may have a different submission date than the original ANDA submission for purposes of evaluating an ANDA applicant's eligibility for 180-day exclusivity for that new drug product and the date from which a first ANDA applicant's compliance with section 505(j)(5)(D)(i)(IV) of the FD&C Act is assessed.

Proposed §§ 314.52(d)(3) and 314.95(d)(3) require that an applicant that submits an amendment or supplement to a 505(b)(2) application or ANDA that contains a paragraph IV certification and seeks approval for a different strength of the drug product must adhere to the timing requirements for notice in §§ 314.52(d)(1) or (d)(2) and 314.95(d)(1) or (d)(2), as applicable. Unlike other amendments and supplements to a 505(b)(2) application or ANDA, an amendment or supplement seeking approval of a different strength may refer to a different listed drug than the listed drug identified in the original 505(b)(2) application or ANDA (see section 505(b)(4)(B) and (j)(2)(D)(ii) of the FD&C Act). Accordingly, we have separately described this type of amendment or supplement to clarify applicable regulatory requirements.

There are a few situations in which the relationship between an acknowledgment letter or paragraph IV acknowledgment letter and the timing of notice for a paragraph IV certification contained in an amendment or supplement to a 505(b)(2) application or ANDA may seem complicated. For example, in the case of a 505(b)(2) or ANDA applicant that submits an original application containing a paragraph III certification to a listed patent and receives an acknowledgment letter (as distinguished from a paragraph IV acknowledgment letter) indicating that the 505(b)(2) application or ANDA has been received for substantive review, if the applicant subsequently submits an amendment containing a paragraph IV certification to a listed patent, the applicant need not wait to receive a paragraph IV acknowledgment letter before sending notice in accordance with § 314.52(d)(1) or § 314.95(d)(1).

Also, we note that FDA may send an acknowledgment letter for certain types of supplements (e.g., a supplement to an ANDA seeking approval for a new strength of a drug product; a 505(b)(2) supplement to an NDA seeking approval for a new indication, new dosage regimen, new route of administration, or a change from prescription use to OTC status for all

conditions of use). However, this practice would not alter the 505(b)(2) or ANDA applicant's statutory obligation to send notice of a paragraph IV certification at the time the supplement is submitted to FDA (and not at the time the paragraph IV acknowledgment letter for the supplement may be received).

We interpret the requirement in proposed § 314.52(d)(1) or § 314.95(d)(1) to send notice of a paragraph IV certification at the same time that the amendment or supplement to the application is submitted to FDA to mean that notice to the NDA holder and each patent owner must be sent on the same day that the amendment or supplement to the application is submitted to FDA. It should be noted that the controlling date for purposes of first applicant eligibility is the date on which the amendment or supplement to the ANDA containing a paragraph IV certification is submitted (i.e., officially received (date-stamped) by the OGD Document Room) as long as notice is timely provided in accordance with the statute. Due to a technical difference in the method by which FDA determines the date of submissions to FDA (using a date of receipt rule) and the date on which an applicant sends notice of a paragraph IV certification to the NDA holder and each patent owner (using a date of mailing rule), these dates may differ. For example, Applicant A submits an amendment containing a paragraph IV certification to its ANDA on August 2 and sends notice of the paragraph IV certification to the NDA holder and each patent owner on that same day. The amendment to the ANDA is date-stamped by the OGD Document Room on August 3. Applicant A has complied with the statutory requirement to send notice of its paragraph IV certification at the same time the amendment or supplement to the ANDA is submitted despite the difference in the date on which the amendment was officially received and the date on which the notice of paragraph IV certification was sent because both the amendment and notice(s) were actually sent on the same day.

If an ANDA applicant does not provide notice of a paragraph IV certification on the same day that an amendment or supplement is submitted, FDA will consider the paragraph IV certification to be effective only as of the date that the applicant has both submitted the amendment or supplement containing the paragraph IV certification and sent the notice (see Purepac Pharmaceutical Co. v. Thompson, 354 F.3d 877 (D.C. Cir. 2004)).

To qualify as a first applicant eligible for 180-day exclusivity under section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act, an applicant must, among other things, submit a paragraph IV certification on the “first day on which a substantially complete application containing a [paragraph IV certification] is submitted.” Because daily electronic updates to the Orange Book generally do not occur until the afternoon (Eastern Standard Time), the opportunity to be a first applicant with respect to a patent that is newly listed in the Orange Book (i.e., to submit an amendment to the ANDA containing a paragraph IV certification and send notice of the paragraph IV certification on that same day) could be affected by, among other things, the time zone in which the ANDA applicant resides. To ensure that all ANDA applicants (irrespective of time zone) have a reasonable opportunity to be a first applicant with respect to a newly listed patent, we are proposing that any notice of paragraph IV certification is invalid if it is sent before the first working day after the day the patent is listed in the Orange Book (see proposed §§ 314.95(b)(2) and 314.94(a)(12)(viii)(C)(1)(ii), discussed in section II.E.4). The term “working day” has the meaning provided in 21 CFR 1.377 (“any day from Monday through Friday, excluding Federal holidays”). This approach is intended to promote equity among ANDA applicants and reduce the burden on industry and on the Agency associated with serial submissions of amendments and multiple notices of paragraph IV certifications related to a newly-issued patent. When a new patent is issued by the PTO, the NDA holder has 30 days

within which to submit the patent information to FDA for listing. An ANDA applicant does not know if or when the patent may be submitted to FDA, and when it is submitted, there may be a delay in the patent's appearance in the Orange Book. Therefore, if an ANDA applicant reasonably believes a patent could be listed for an RLD, it will often submit a paragraph IV certification to FDA and send notice to the NDA holder and patent owner each day during the 30-day period after issuance of the new patent. ANDA applicants have adopted this practice in an attempt to satisfy the certification and notice requirements on the first date on which the patent is listed in the Orange Book and thus qualify as a first applicant. FDA's proposal is intended to eliminate the need for these burdensome serial certifications.

The following example illustrates our approach: The NDA holder submits Form FDA 3542 to the Office of Generic Drugs, Document Room, Attention: Orange Book Staff, within 30 days after issuance of the '123 patent claiming the drug product Litigatolol. Form FDA 3542 is date-stamped by the OGD Document Room on Friday, August 5 and listed in the Orange Book, which is updated at 3 p.m. Eastern Standard Time on that date. Applicant B and Applicant C have submitted ANDAs for Litigatolol and have received acknowledgment letters indicating that their ANDAs have been received for substantive review. Applicant B is located in California and submits an amendment to its ANDA containing a paragraph IV certification to the '123 patent and sends notice to the NDA holder and each patent owner late in the afternoon, Pacific Time, on Friday, August 5. Applicant C is located in New Jersey and would have been unable to submit an amendment to its ANDA containing a paragraph IV certification to the '123 patent and send notice to the NDA holder and each patent owner before the end of the working day on Friday, August 5. Applicant C submits the amendment and sends notice on Monday, August 8. Prior to these amendments, no ANDA had contained a paragraph IV certification to a patent

listed for Litigatolol. Applicant B prematurely submitted its amendment containing a paragraph IV certification, and its notice of paragraph IV certification is invalid because it was sent before the first full working day after the patent is listed in the Orange Book. Only Applicant C has submitted the first substantially complete ANDA containing a paragraph IV certification for purposes of first applicant eligibility.

It should be noted that if there is a delay between FDA's receipt of new patent information and publication of the patent information in the Orange Book, the actual date of publication of the patent information in the Orange Book provides the date from which the validity of the ANDA applicant's notice of paragraph IV certification will be assessed for purposes of first applicant eligibility (compare section II.D.3 regarding determination of a 505(b)(2) or ANDA applicant's patent certification obligations and the availability of a 30-month stay based on patent information in FDA's possession).

II.D.1.c. Certification of provision of notice. We are proposing to amend §§ 314.52(b) and 314.95(b) by revising and redesignating certain text as new paragraph (b)(3). Proposed §§ 314.52(b)(3) and 314.95(b)(3) describe the current requirement for 505(b)(2) and ANDA applicants, respectively, to amend their applications at the time that they provide notice of a paragraph IV certification to include a statement certifying that notice has been provided to the NDA holder and each patent owner as required by §§ 314.52(a) and 314.95(a) and has met the content requirements for notice of a paragraph IV certification as described in §§ 314.52(c) and 314.95(c). We are proposing to clarify that a copy of the notice of paragraph IV certification itself does not need to be submitted to FDA in the amendment.

We describe acceptable methods for delivery of notice of paragraph IV certification and documentation of timely delivery and receipt of such notice in section II.D.4.

II.D.2. Notice Required for All Paragraph IV Certifications

The MMA requires applicants submitting 505(b)(2) applications and ANDAs to provide notice for all paragraph IV certifications submitted to FDA on or after August 18, 2003, regardless of whether the applicant had previously given notice of a paragraph IV certification contained in its application or an amendment or supplement to the application (see section 505(b)(3)(B) and (j)(2)(B)(ii) of the FD&C Act).

We are proposing to require a 505(b)(2) or ANDA applicant to provide a new notice of paragraph IV certification to a patent for which it previously had provided notice if the applicant submits an amendment or supplement to the 505(b)(2) application or ANDA for certain changes to the proposed product that should be accompanied by a new patent certification (see section II.F).

II.D.3. Contents of Notice

We are proposing to revise §§ 314.52(c) and 314.95(c) regarding the contents of notice of a paragraph IV certification to incorporate requirements added by the MMA and to support the efficient enforcement of our regulations. We note, however, that the Agency neither assesses the adequacy of the contents of a 505(b)(2) or ANDA applicant's notice of paragraph IV certification nor the applicant's stated basis for certifying that a listed patent is invalid, unenforceable, or will not be infringed by its proposed drug product. In our final rule implementing the patent and exclusivity provisions of the Hatch-Waxman amendments, we stated that "the agency does not have the expertise or the desire to become involved in issues concerning patent law and sufficiency of notice. ... Disputes involving the sufficiency of the notice [i.e., the detailed statement of the factual and legal basis behind the applicant's opinion that the patent is invalid, unenforceable, or not infringed] must be resolved by the applicant,

patent owner, and holder of the approved application rather than by action on the part of FDA” (59 FR 50338 at 50349, October 3, 1994).

We also are revising §§ 314.52(c) and 314.95(c) to require the 505(b)(2) or ANDA applicant to cite section 505(b)(3)(D) and (j)(2)(B)(iv), respectively, as amended by the MMA, in the notice of paragraph IV certification.

Table 7 summarizes the proposed changes related to content of a notice of paragraph IV certification.

Table 7.--Highlights of Proposed Changes Regarding Content of a Notice of Paragraph IV Certification¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Content of a notice (§§ 314.52(c)) and 314.95(c))</u></p> <ul style="list-style-type: none"> • The 505(b)(2) or ANDA applicant must cite section 505(b)(3)(B) or 505(j)(2)(B)(ii) of the FD&C Act, as appropriate, and the notice must also include, but not be limited to, the following information: <ul style="list-style-type: none"> --(1) A statement that a 505(b)(2) application submitted by the applicant has been filed by FDA; or <ul style="list-style-type: none"> a statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability (BA) or bioequivalence (BE) data or information. --(2) The NDA or ANDA number. --(3) The established name, if any, of the proposed drug product. --(4) The active ingredient, strength, and dosage form of the proposed drug product. --(5) The patent number and expiration date, as submitted to the Agency or as known to the applicant, of each patent alleged to be invalid, unenforceable, or not infringed. --(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. --(7) If the applicant does not reside or have a place of business in the U.S., the name and address of an agent in the U.S. authorized to accept service of process for the applicant. 	<p><u>Content of a notice (§§ 314.52(c)) and 314.95(c))</u></p> <ul style="list-style-type: none"> • The 505(b)(2) or ANDA applicant must cite section 505(b)(3)(D) or 505(j)(2)(B)(iv) of the FD&C Act, as appropriate, and the notice must also include, but is not limited to, the following information: <ul style="list-style-type: none"> --(1) A statement that a 505(b)(2) application that contains any required BA or BE data has been submitted by the applicant and filed by FDA; or <ul style="list-style-type: none"> a statement that FDA has received an ANDA submitted by the applicant containing any required BA or BE data or information. --(2) The NDA or ANDA number. --(3) A statement that the applicant has received the acknowledgment letter or paragraph IV acknowledgment letter for the 505(b)(2) application or ANDA. --(4) The established name, if any, of the proposed drug product. --(5) The active ingredient, strength, and dosage form of the proposed drug product. --(6) The patent number and expiration date of each patent on the list alleged to be invalid, unenforceable, or not infringed. --(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. --(8) If the applicant alleges that the patent will not be infringed and may later decide to file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) and 505(j)(5)(C) of the FD&C Act, then the notice must be accompanied by an offer of confidential access to the 505(b)(2) application or ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification. --(9) If the applicant does not reside or have a place of business in the U.S., the name and address of an agent in the U.S. authorized to accept service of process for the applicant.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.D.3.a. Statement that any required bioavailability or bioequivalence studies for a 505(b)(2) application have been submitted. The MMA amended the FD&C Act to require that

the notice of paragraph IV certification for a 505(b)(2) application include a statement that “an application that contains data from bioavailability or bioequivalence studies” has been submitted to FDA (section 505(b)(3)(D)(i) of the FD&C Act). This statutory provision parallels the content requirements for notice of paragraph IV certification for an ANDA (see section 505(j)(2)(B)(iv)(I) of the FD&C Act). Consistent with our previous implementation of the statutory requirement for ANDAs in § 314.95(c), proposed § 314.52(c)(1) requires that a notice of a paragraph IV certification for a 505(b)(2) application state that data from “any required bioavailability or bioequivalence studies” (emphasis added) have been submitted. This qualifier reflects that FDA may exercise its scientific judgment to determine what bioavailability and bioequivalence studies may be needed for certain 505(b)(2) applications and ANDAs (see, e.g., § 314.54(a)(1) and (a)(2) (citing §§ 314.50(d)(3) and 320.21(a)(2) and (f)); compare § 320.21(b)(2)).

A 505(b)(2) application may seek to rely upon non-product-specific published literature or other studies necessary for approval for which the applicant has no right of reference or use. This type of 505(b)(2) application generally would not require studies showing relative bioavailability or bioequivalence because the 505(b)(2) application is not relying upon the Agency’s finding of safety and/or effectiveness for a listed drug. In the absence of a listed drug, there is not likely to be a specific drug for use as a comparator in a relative bioavailability or bioequivalence study. However, such a 505(b)(2) application must establish that reliance on the studies described in the literature is scientifically appropriate. Further, a 505(b)(2) application that did not rely upon a listed drug would not require a patent certification or statement, and thus there would be no occasion for a notice of paragraph IV certification.

II.D.3.b. Statement confirming receipt of an acknowledgment letter or a paragraph IV acknowledgment letter. We are proposing to revise §§ 314.52(c)(3) and 314.95(c)(3) to add a new requirement for 505(b)(2) and ANDA applicants, respectively, to facilitate compliance with and enforcement of section 505(b)(3)(B)(i), (b)(3)(B)(ii), (j)(2)(B)(ii)(I), and (j)(2)(B)(ii)(II) of the FD&C Act regarding the timing of notice of paragraph IV certification. Proposed §§ 314.52(c)(3) and 314.95(c)(3) require a 505(b)(2) and ANDA applicant, respectively, to include a statement in its notice of paragraph IV certification that the applicant has received an acknowledgment letter or a paragraph IV acknowledgment letter for its 505(b)(2) application or ANDA. This requirement is intended to ensure that a notice of paragraph IV certification is not sent before FDA has determined that the 505(b)(2) application or ANDA containing the certification is acceptable for substantive review and has issued an acknowledgment letter or a paragraph IV acknowledgment letter (see section II.D.1.a).

II.D.3.c. Documentation that paragraph IV certification was submitted and notice was sent only for patents listed in the Orange Book. We are proposing to revise §§ 314.52(c)(6) and 314.95(c)(6) to specify that notice of a paragraph IV certification (and therefore the underlying paragraph IV certification as well) must only be sent for a patent that is listed in the Orange Book for the listed drug(s) relied upon for a 505(b)(2) application or for the RLD for an ANDA. We are proposing to add the phrase “on the list” to proposed §§ 314.52(c)(6) and 314.95(c)(6) to qualify the patents for which a notice of paragraph IV certification must be sent.

As discussed in section II.D.4.b, we are proposing to require an ANDA applicant to include a dated printout of the Orange Book entry for the RLD that includes the patent that is the subject of the notice of paragraph IV certification in its amendment certifying that notice of paragraph IV certification has been sent and documenting that notice has been received (see

proposed § 314.95(e)). A 505(b)(2) applicant may elect to submit a copy of the Orange Book patent listing for the listed drug(s) relied upon with its 505(b)(2) application, amendment, or supplement containing a paragraph IV certification to describe the applicant's understanding of the most current patent information listed in the Orange Book at the time of submission. We note, however, that a 505(b)(2) or ANDA applicant's patent certification obligations and the availability of a 30-month stay under section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act are determined based on patent information in FDA's possession, even if such information is not accurately listed in the Orange Book (see Teva Pharms., USA, Inc. v. Leavitt, 548 F.3d 103, at 105 (D.C. Cir. 2008) ("FDA insists reality matters")).

In addition, we are proposing to delete the phrase "as submitted to the agency or as known to the applicant" from §§ 314.52(c)(6) and 314.95(c)(6), as this phrase is over-inclusive. It does not accurately describe the universe of patents for which a paragraph IV certification may be submitted and thus is inapplicable to the content requirements for notice of a paragraph IV certification. Although an applicant may submit a certification pursuant to section 505(b)(2)(A)(i) or 505(j)(2)(A)(vii)(I) of the FD&C Act ("paragraph I certification") with respect to patent information that has not been filed with FDA and is not listed in the Orange Book, such a patent could not be the basis for a paragraph IV certification.

II.D.3.d. Offer of confidential access accompanying notice. The MMA established conditions under which a 505(b)(2) or ANDA applicant may bring a declaratory judgment action to obtain "patent certainty" (i.e., obtain a judicial determination of noninfringement, invalidity, or unenforceability) with respect to a listed patent for which it has given notice of a paragraph IV certification but has not been sued by the NDA holder or any patent owner within the statutory timeframe (see section 505(c)(3)(D) and (j)(5)(C) of the FD&C Act). As a precondition to filing

an action for declaratory judgment to establish patent noninfringement (as distinguished from patent invalidity or unenforceability), the applicant must provide a document offering the NDA holder and each patent owner confidential access to the 505(b)(2) application or ANDA for the sole and limited purpose of assessing patent noninfringement (see section 505(c)(3)(D)(i)(III) and (j)(5)(C)(i)(III) of the FD&C Act). Because this offer of confidential access, if made, is required to accompany the notice of paragraph IV certification, we are proposing to revise §§ 314.52(c) and 314.95(c) to reference the statutory requirement for an offer of confidential access (see section 505(c)(3)(D)(i)(I)(cc) and (j)(5)(C)(i)(I)(cc) of the FD&C Act). Our proposed regulations do not otherwise address the offer of confidential access because the process for seeking a declaratory judgment does not involve FDA.

II.D.4. Documentation of Timely Sending and Receipt of Notice

We are proposing to revise §§ 314.52(e) and 314.95(e) to clarify the requirements for submission of an amendment to a 505(b)(2) application or ANDA, respectively, containing documentation of timely sending of notice of paragraph IV certification and confirmation of receipt of same by the NDA holder and each patent owner. In addition, we are proposing to revise §§ 314.52 and 314.95 to expand the list of acceptable delivery methods that may be used to send notice of paragraph IV certification to the NDA holder and each patent owner. These proposed revisions are intended to facilitate compliance with the statutory requirements regarding timing of notice of paragraph IV certification and related regulatory provisions.

Table 8 summarizes the proposed changes regarding documentation of timely sending and receipt of notice of paragraph IV certification:

Table 8.--Highlights of Proposed Changes Regarding Documentation of Timely Sending and Receipt of Notice of Paragraph IV Certification¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Notice of certification (§§ 314.52(a) and 314.95(a))</u></p> <ul style="list-style-type: none"> • 505(b)(2) or ANDA applicant must send notice of paragraph IV certification by registered or certified mail, return receipt requested, to each patent owner and the NDA holder. 	<p><u>Notice of certification (§§ 314.52(a) and 314.95(a))</u></p> <ul style="list-style-type: none"> • 505(b)(2) or ANDA applicant must send notice of paragraph IV certification by registered or certified mail, return receipt requested, or by a designated delivery service, to each patent owner and the NDA holder. • 505(b)(2) or ANDA applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.
<p><u>Documentation of receipt of notice (§§ 314.52(e) and 314.95(e))</u></p> <ul style="list-style-type: none"> • Applicant must amend its 505(b)(2) application or ANDA to document the date of receipt of the notice of paragraph IV certification by each patent owner and NDA holder provided the notice. • Applicant must include a copy of the return receipt or other similar evidence of the date the notification was received. -- FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. • An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. 	<p><u>Documentation of timely sending and receipt of notice (§§ 314.52(e) and 314.95(e))</u></p> <ul style="list-style-type: none"> • Applicant must amend its 505(b)(2) application or ANDA to provide documentation of the date of receipt of the notice of paragraph IV certification by each patent owner and NDA holder provided the notice. --FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided notice. -- Amendment must be submitted to FDA within 30 days after the last date on which notice was received by a patent owner or NDA holder. • Amendment also must include adequate documentation that notice was sent on a date that complies with the timeframe required by § 314.52(b) or (d) or § 314.95(b) or (d), as applicable. --FDA will accept a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as adequate documentation of the date of delivery. • An ANDA applicant's amendment must include a dated printout of the Orange Book entry for the RLD that includes the patent that is the subject of the paragraph IV certification. • An applicant may rely on another form of documentation only if FDA has agreed in advance.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.D.4.a. Acceptable methods of sending notice of paragraph IV certification. A

505(b)(2) or ANDA applicant currently is required to send notice of a paragraph IV certification to the NDA holder and each patent owner by registered or certified mail, return receipt requested, unless FDA agrees in advance to another method of delivery (see §§ 314.52(a) and (e) and 314.95(a) and (e)). We are proposing to revise §§ 314.52(a) and (e) and 314.95(a) and (e) to provide applicants with the option of sending notice of paragraph IV certification by a designated delivery service, as defined in proposed §§ 314.52(g)(1) and 314.95(g)(1). Section 505(b)(2) and ANDA applicants often request permission to send notice of a paragraph IV certification by a major commercial delivery service instead of the U.S. Postal Service (for example, to send notice of a paragraph IV certification to a patent owner who resides outside of the United States). Because we routinely grant these requests, we are proposing to amend our regulations to provide the option to all 505(b)(2) and ANDA applicants to send notice of paragraph IV certification by the U.S. Postal Service or a designated delivery service. We propose to define a “designated delivery service” in §§ 314.52(g)(1) and 314.95(g)(1) to mean any delivery service provided by a trade or business that the Agency determines: (1) Is available to the general public throughout the United States; (2) records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and (3) provides overnight or 2-day delivery service throughout the United States.

This proposed definition is adapted from definition of “designated delivery service” in 26 U.S.C. 7502(f)(2) (governing timely mailing treated as timely filing and paying by the IRS). As noted in proposed §§ 314.52(g)(2) and 314.95(g)(2), FDA will periodically issue guidance describing designated delivery services that meet these criteria.

Our proposal to revise §§ 314.52(a) and (e) and 314.95(a) and (e) to provide applicants with the option of sending notice of paragraph IV certification by a designated delivery service, as defined in proposed §§ 314.52(g)(1) and 314.95(g)(1), differs from an earlier proposal to provide additional methods of sending notice of paragraph IV certification (see “New Drugs for Human Use; Clarification of Requirements for Patent Holder Notification; Proposed Rule” 63 FR 11174; March 6, 1998) (Patent Holder Notification proposed rule). The Patent Holder Notification proposed rule would have permitted a 505(b)(2) or ANDA applicant to send notice of paragraph IV certification “by mail or personal delivery” (including overnight delivery service, electronic mail, and facsimile) if the applicant obtained a verification of receipt. We received comments objecting to certain aspects of the Patent Holder Notification Proposed Rule--in particular, notice by electronic methods of delivery such as electronic mail or facsimile--and withdrew the proposed rule (see “New Drugs for Human Use; Clarification of Requirements for Patent Holder Notification; Withdrawal” 65 FR 12154; March 8, 2000) (Withdrawal of Patent Holder Notification proposed rule). With respect to notification by overnight delivery service, two comments on the Patent Holder Notification proposed rule supported this alternate method of delivery if a signed verification of receipt of notice by the NDA holder or each patent owner was provided (see Docket No. FDA-1997-P-0417-0011 and FDA-1997-P-0417-0012, available at <http://www.regulations.gov>). Another comment objected to notification by overnight delivery service because receipt of bulk deliveries (containing multiple envelopes and packages) to large corporations is acknowledged by a single signature. This commenter expressed concern that an overnight delivery service envelope containing a notice of paragraph IV certification may not ensure timely receipt by a responsible person. Given that receipt of notice of paragraph IV certification begins a statutory 45-day period within which a patent infringement action must be

filed to obtain, under certain circumstances, a 30-month stay, a signature acknowledging receipt of the specific envelope was preferred by this commenter (see Docket No. FDA-1997-P-0417-0010, available at <http://www.regulations.gov>).

In light of the frequency with which FDA receives requests to send notice by overnight delivery services, we invite comment on our current proposal to provide applicants with the option of sending notice of paragraph IV certification by a designated delivery service, as defined in proposed §§ 314.52(g)(1) and 314.95(g)(1).

We also are proposing to add §§ 314.52(a)(4) and 314.95(a)(4) and revise §§ 314.52(e) and 314.95(e) to clarify that a 505(b)(2) or ANDA applicant may send notice of paragraph IV certification by an alternative method (i.e., a method other than registered or certified mail, return receipt requested, or a designated delivery service) only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

In addition, we are proposing to revise the introductory text of § 314.52(a) to refer to each patent that claims the listed drug or drugs relied upon or that claims a use for such listed drug or drugs and for which the applicant submits a paragraph IV certification. This revision is proposed for clarity and does not represent a substantive change.

II.D.4.b. Amendment documenting timely sending and confirmation of receipt of notice of paragraph IV certification. We are proposing to revise §§ 314.52(e) and 314.95(e) to facilitate implementation of section 505(b)(3)(B)(i), (b)(3)(B)(ii), (j)(2)(B)(ii)(I), and (j)(2)(B)(ii)(II) of the FD&C Act and for the efficient enforcement of the FD&C Act.

A 505(b)(2) or ANDA applicant that has submitted one or more paragraph IV certifications currently must submit an amendment to its application documenting the date on which notice of paragraph IV certification was received by the NDA holder and each patent

owner (see §§ 314.52(e) and 314.95(e)). As discussed in section II.D.1.b, the MMA amended the FD&C Act to require that a 505(b)(2) and ANDA applicant provide notice of a paragraph IV certification in accordance with the timeframes described in section 505(b)(3)(B)(i), (b)(3)(B)(ii), (j)(2)(B)(ii)(I), and (j)(2)(B)(ii)(II) of the FD&C Act (see proposed §§ 314.52(b) and (d) and 314.95(b) and (d)). Our proposed revisions to §§ 314.52(e) and 314.95(e) require a 505(b)(2) and ANDA applicant, respectively, to establish compliance with this statutory requirement by also submitting in its amendment documentation that the notice of paragraph IV certification was sent on a date that complies with the timeframe required by § 314.52(b) or (d) or § 314.95(b) or (d), as applicable. For administrative efficiency, we are proposing to require that a 505(b)(2) or ANDA applicant submit the amendment containing documentation of timely sending and receipt of notice of paragraph IV certification within 30 days after the last date on which notice was received by a person described in § 314.52(a) or § 314.95(a), respectively.

The proposed requirement for documentation that notice of paragraph IV certification was timely sent can be satisfied by submitting a copy of the registered mail receipt or certified mail receipt issued by the U.S. Postal Service that bears a postmark documenting the date of mailing or by submitting a copy of the receipt from a designated delivery service, as defined in proposed §§ 314.52(g) and 314.95(g). With respect to documentation of the date of receipt of notice of paragraph IV certification, we are proposing to revise §§ 314.52(e) and 314.95(e) to include acceptance of signature proof of delivery by a designated delivery service as adequate documentation. A single document may be adequate to document both timely sending and receipt of notice of paragraph IV certification if it contains the information required by proposed §§ 314.52(e) and 314.95(e).

In addition, we are proposing to require that ANDA applicants include in their amendment a dated printout of the Orange Book entry for the RLD that includes the patent that is the subject of the notice of paragraph IV certification. This requirement is intended to ensure that a paragraph IV certification that may qualify an ANDA applicant for 180-day exclusivity is submitted only for a listed patent and is not prematurely or inappropriately sent before the first working day after the day the patent is listed in the Orange Book (see proposed §§ 314.95(b)(2) and 314.94(a)(12)(viii)(C)(1)(ii)).

The following example illustrates our approach: The NDA holder timely submits Form FDA 3542 to the Office of Generic Drugs, Document Room, Attention: Orange Book Staff, at 4 p.m., Eastern Standard Time, on the 30th day after issuance of the '456 patent claiming the drug product Procrastinadipine. Form FDA 3542 is date-stamped by the Office of Generic Drugs, Document Room on Friday, October 1 and listed in the Orange Book on the afternoon of Monday, October 4. Applicant D and Applicant E have submitted ANDAs for Procrastinadipine and each has received an acknowledgment letter indicating that its ANDA has been received for substantive review.

Applicant D is aware that the '456 patent was issued by the PTO on September 1 and understands that for the '456 patent to be timely filed under section 505(c)(2) of the FD&C Act, the NDA holder must file the patent information with FDA no later than October 1. Applicant D submits an amendment to its ANDA containing a paragraph IV certification to the '456 patent and sends notice to the NDA holder and each patent owner on October 1 in an effort to have submitted the first substantially complete ANDA containing a paragraph IV certification to a patent listed for Procrastinadipine. However, Applicant D is unable to submit the required printout (see proposed § 314.95(b)(2)) of the Orange Book entry for the RLD that includes the

patent that is the subject of the paragraph IV certification because the '456 patent has not yet been listed in the Orange Book. Applicant E submits on Tuesday, October 5 (i.e., the first working day after the day the patent is listed in the Orange Book) an amendment to its ANDA containing a paragraph IV certification to the '456 patent and the required printout of the Orange Book entry and sends notice to the NDA holder and each patent owner on that same day.

Prior to these amendments, no ANDA had contained a paragraph IV certification to a patent listed for Procrastinadipine. Applicant D's notice of paragraph IV certification is premature and thus invalid because the '456 patent had not yet been listed in the Orange Book. Only Applicant E has submitted the first substantially complete ANDA containing a paragraph IV certification for purposes of first applicant eligibility.

II.D.5. Administrative Consequence for Late Notice

The MMA does not specify a consequence for 505(b)(2) or ANDA applicants that do not send notice of a paragraph IV certification within the timeframe required by the FD&C Act (i.e., within 20 days after the date of the postmark on the paragraph IV acknowledgment letter or on the date that an amendment or supplement containing a paragraph IV certification is submitted to FDA). In response to our Request for MMA Comments, we received comments suggesting that we create an administrative consequence for late notice (see, e.g., PhRMA MMA Comment at 1 to 2). In light of the importance of the timing of sending notice of paragraph IV certification to the statutory scheme, we agree that it is appropriate to propose an administrative consequence for ANDA applicants who are late in providing notice.

After considering several suggestions for administrative consequences, including those submitted to us in response to our Request for MMA Comments, we are proposing to address ANDA applicants that fail to timely provide notice of a paragraph IV certification by moving

forward the date of submission of the ANDA by the number of days beyond the required time frame that the applicant delayed in sending its notice (see proposed § 314.101(b)(4)).

Consequently, an ANDA applicant may lose its first applicant status and thus its eligibility for 180-day exclusivity as a result of providing late notice (see section 505(j)(5)(B)(iv) of the FD&C Act), if another applicant submits a substantially complete ANDA containing a paragraph IV certification on the same first day and provides timely notice. Also, an ANDA applicant that fails to timely provide notice of paragraph IV certification may experience a delay in the review queue for its ANDA consistent with the revised date of submission. We note that this proposed administrative consequence would not reduce the 30-month timeframe set forth in section 505(j)(5)(D)(i)(I)(aa)(BB) and (j)(5)(D)(i)(IV) of the FD&C Act in the forfeiture calculus for a first applicant; rather, the 30-month period would begin on the revised date of submission.

We believe that the proposed administrative consequence for ANDA applicants appropriately balances the purposes served by the requirement for timely notice of paragraph IV certifications with the legislative goal of speeding the availability of lower cost alternatives to approved drugs. Certain options we considered as alternatives did not seem to provide as measured a balance. For example, we considered deeming paragraph IV certifications for which notice had been provided after the statutory timeframe to not be “lawfully maintained” (see section 505(j)(5)(B)(iv)(bb) of the FD&C Act). Under this interpretation, however, an ANDA applicant would certainly lose its eligibility for 180-day exclusivity as a result of sending late notice, regardless of the amount of time its notice was delayed (e.g., even if its notice were one day late). We decline to adopt this approach because it seems disproportionately punitive.

We are not proposing a similar consequence for 505(b)(2) applicants that fail to timely provide notice of a paragraph IV certification because 505(b)(2) applicants are not eligible for

180-day exclusivity and we are unable to extend the review clock as an administrative consequence for an NDA (including a 505(b)(2) application) subject to the Prescription Drug User Fee Act Reauthorization Performance Goals and Procedures (see <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm>; see also 21 CFR 314.100). As described below, we considered other possible administrative consequences for any 505(b)(2) applicants that fail to provide notice of a paragraph IV certification within the statutory timeframe; however, we are declining to propose an administrative consequence at this time.

The implications of late notice of a paragraph IV certification by a 505(b)(2) applicant differ from those of an ANDA applicant that may otherwise be eligible for 180-day exclusivity. A 505(b)(2) application that contains a paragraph IV certification could not be approved until the 505(b)(2) applicant had provided notice of its paragraph IV certification to the NDA holder and each patent owner and the respective 45-day periods for each recipient of notice had expired without the filing of a legal action for patent infringement (see § 314.107(f)(2)). A 505(b)(2) applicant that provides late notice of a paragraph IV certification risks that the NDA holder or patent owner will file an action for patent infringement within the 45-day period after notice, and that any resultant 30-month stay will delay approval by a period of time commensurate with the 505(b)(2) applicant's delay in providing notice of its paragraph IV certification. We considered the suggestion, submitted in response to our Request for MMA Comments, that we "creat[e] an automatic regulatory presumption which could be used by the court hearing the patent infringement action that the ANDA or 505(b)(2) applicant 'failed to reasonably cooperate in expediting the action' within the meaning of [section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act]" (see PhRMA MMA Comment at 2). However, we decline to propose this approach

because it is not necessary to properly implement the statutory goal of adequate notice and opportunity to defend certain intellectual property rights prior to approval.

II.E. Amended Patent Certifications (Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii))

We are proposing to revise §§ 314.50(i)(6) and 314.94(a)(12)(viii) regarding submission of amended patent certifications by 505(b)(2) and ANDA applicants, respectively, to reflect revisions to the FD&C Act made by the MMA and for the efficient enforcement of the FD&C Act. A 505(b)(2) or ANDA applicant would be required to submit an amended patent certification to provide, for example, a certification to a recently issued patent listed by the NDA holder after submission of a 505(b)(2) application or ANDA that relies upon the listed drug, or to change its certification to a patent for which the applicant had previously submitted a patent certification. As discussed in this section of the document, submission of an amended patent certification also would be required for a reissued patent and for a revision to a prior certification in the event that a patent or patent information has been withdrawn from listing in the Orange Book.

We are proposing to revise the introductory text of § 314.94(a)(12)(viii) to remove the provision that restricts an ANDA applicant from amending a paragraph IV certification to a paragraph III certification in certain circumstances. Currently, § 314.94(a)(12)(viii) provides that an ANDA applicant that has submitted a paragraph IV certification may not amend its patent certification to a paragraph III certification (delaying approval until the date on which such patent will expire) if a patent infringement action has been filed against another applicant that had submitted a paragraph IV certification. The current regulation provides that an ANDA applicant is permitted to amend its patent certification to a paragraph III certification in these circumstances only if the Agency has determined that no applicant is entitled to 180-day

exclusivity or the patent expired while patent infringement litigation was pending or before the end of the 180-day exclusivity period. We have determined, however, that it is not necessary to restrict submission of an amended patent certification under these circumstances because 180-day exclusivity does not extend beyond patent expiry. Accordingly, an applicant that amended its paragraph IV certification to a paragraph III certification would not be eligible for approval until patent expiration and thus would not undermine a first applicant's 180-day exclusivity as to that patent. The MMA specifically provides that a first applicant's 180-day exclusivity would, in any event, terminate upon expiration of all of the patents as to which the applicant submitted a paragraph IV certification qualifying it for 180-day exclusivity (see section 505(j)(5)(D)(i)(VI) of the FD&C Act; see also § 314.94(a)(12)(viii)).

There are several circumstances in which amending to a paragraph III certification is appropriate, including when an applicant is no longer seeking approval before the patent expires or when required by the terms of a settlement agreement between parties in patent infringement litigation. This proposal would facilitate amendment of paragraph IV certifications to paragraph III certifications in such circumstances.

We also are proposing to revise §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii) to require that a 505(b)(2) or ANDA applicant submit an amended patent certification as an amendment to its pending application (including a supplemental 505(b)(2) application or supplemental ANDA (see §§ 314.70(i) and 314.97(c), respectively)) and not by letter. This requirement will facilitate appropriate management of amended patent certifications.

Table 9 summarizes the proposed changes regarding amended patent certifications:

Table 9.--Highlights of Proposed Changes Regarding Amended Patent Certifications¹

Current Regulations	Proposed Revisions to Regulations
<u>Amended Certifications (§§ 314.50(i)(6) and 314.94(a)(12)(viii))</u> <ul style="list-style-type: none"> Amended patent certification must be submitted as an amendment to a pending 505(b)(2) application or ANDA or by letter to an approved application. 	<u>Amended Certifications (§§ 314.50(i)(6) and 314.94(a)(12)(viii))</u> <ul style="list-style-type: none"> Amended patent certification must be submitted as an amendment to the 505(b)(2) application or ANDA and may no longer be submitted by letter.
<u>Amended Certifications (§ 314.94(a)(12)(viii) only)</u> <ul style="list-style-type: none"> ANDA applicants restricted from amending a paragraph IV certification to a paragraph III certification in certain circumstances when another ANDA applicant has been sued for patent infringement. 	<u>Amended Certifications (§ 314.94(a)(12)(viii) only)</u> <ul style="list-style-type: none"> Deletion of restriction on ANDA applicants from amending a paragraph IV certification to a paragraph III certification.
<u>After a Finding of Infringement (§§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A))</u> <ul style="list-style-type: none"> Change from paragraph IV certification to paragraph III certification required after a final judgment is entered finding the patent to be infringed. Provision applies if patent infringement action initiated within 45 days of receipt of notice of paragraph IV certification. 	<u>After a Finding of Infringement (§§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A))</u> <ul style="list-style-type: none"> Change from paragraph IV certification to paragraph III certification required after court enters final decision from which no appeal has been or can be taken, or signs settlement order or consent decree with a finding of infringement (unless the patent also is found invalid). An applicant may instead provide a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) with respect to a method-of-use patent if the 505(b)(2) application or ANDA is amended such that the applicant is no longer seeking approval for a method of use claimed by the patent. Provision applies if patent infringement action initiated after receipt of notice of paragraph IV certification, irrespective of whether the action is brought within the 45-day period.

Table 9.--Highlights of Proposed Changes Regarding Amended Patent Certifications¹

Current Regulations	Proposed Revisions to Regulations
<p><u>After Removal of a Patent from the List (§§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B))</u></p> <ul style="list-style-type: none"> • If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent must amend its certification. • A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. • Applicant must submit a “no relevant patents” certification or, if other relevant patents claim the drug, must amend the patent certification to refer only to those relevant patents. 	<p><u>After Request to Remove a Patent or Patent Information from the List (§§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B))</u></p> <ul style="list-style-type: none"> • If the list reflects that an NDA holder has requested that a patent be removed from the list and: <ul style="list-style-type: none"> --no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will be removed and any applicant with a pending 505(b)(2) application or ANDA (including a tentatively approved 505(b)(2) application or ANDA) who has certified to that patent must submit an amendment to withdraw the certification. --one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent shall remain listed until any 180-day exclusivity is extinguished. • If one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to a patent that has been reissued, then the first applicant must submit a paragraph IV certification to the reissued patent within 30 days of listing to have lawfully maintained its paragraph IV certification for purposes of eligibility for 180-day exclusivity. • A 505(b)(2) applicant is not required to provide or maintain a certification to a patent that remains listed only for purposes of a first applicant’s 180-day exclusivity. • After any applicable 180-day exclusivity period has ended, the patent will be removed and any pending ANDA (including a tentatively approved ANDA) that contains a certification to the patent must be amended to withdraw the certification. • If removal of a patent from the list results in no patents listed for the listed drug(s) identified in the 505(b)(2) application or ANDA, the applicant must submit an amended certification reflecting that there are no listed patents.

Table 9.--Highlights of Proposed Changes Regarding Amended Patent Certifications¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Late submission of patent information</u> (§§ 314.50(i)(4) and 314.94(a)(12)(vi))</p> <ul style="list-style-type: none"> • If a patent on the listed drug is issued and the NDA holder for the listed drug does not submit the required information on the patent within 30 days of patent issuance, an applicant who submitted a 505(b)(2) application or an ANDA for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification. • An applicant whose 505(b)(2) application or ANDA is submitted after a late submission of patent information, or whose pending 505(b)(2) application or ANDA was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, must submit a certification under (§ 314.50(i)(1)(i) or § 314.94(a)(12)(i) or a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) as to that patent. <p><u>Patents Claiming the Drug Substance, Drug Product, or Method of Use (§§ 314.50(i)(1)(i)(A) and 314.94(a)(12)(i)(A))</u></p> <ul style="list-style-type: none"> • A 505(b)(2) application and ANDA are required to contain a patent certification or statement for each patent issued by the PTO that, in the opinion of the applicant and to the best of its knowledge, claims the listed drug relied upon or RLD or that claims an approved use for such drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b) and (c) of the FD&C Act and § 314.53. 	<p><u>Untimely filing of patent information</u> (§§ 314.50(i)(4) and 314.94(a)(12)(vi))</p> <ul style="list-style-type: none"> • (see Table 3) <p><u>Patents Claiming the Drug Substance, Drug Product, or Method of Use (§§ 314.50(i)(1)(i)(A) and 314.94(a)(12)(i)(A))</u></p> <ul style="list-style-type: none"> • (No substantive revisions) <p><u>Other Amendments (§§ 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(viii)(C)(1)(ii))</u></p> <ul style="list-style-type: none"> • Except as provided in §§ 314.50(i)(4) and (i)(6)(iii)(B) and 314.94(a)(12)(vi) and (a)(12)(viii)(C)(2)), an applicant must submit a patent certification or statement if, after submission of the 505(b)(2) application or ANDA, a new patent is issued by the PTO that, in the opinion of the applicant and to the best of its knowledge, claims the listed drug or RLD or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the FD&C Act and § 314.53. • For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

Table 9.--Highlights of Proposed Changes Regarding Amended Patent Certifications¹

Current Regulations	Proposed Revisions to Regulations
<u>Other Amendments (§§ 314.50(i)(6)(iii)(A) and 314.94(a)(12)(viii)(C)(1))</u> <ul style="list-style-type: none"> [Amended patent certification required upon patent expiration under existing requirement for submission of amended certification if, at any time before approval, the submitted certification is no longer accurate.] 	<u>Other Amendments (§§ 314.50(i)(6)(iii)(A)(1) and 314.94(a)(12)(viii)(C)(1)(i))</u> <ul style="list-style-type: none"> [Upon patent expiration, FDA will consider the 505(b)(2) or ANDA applicant to have constructively changed its patent certification to a paragraph II certification.]
<u>Other Amendments (§§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2))</u> <ul style="list-style-type: none"> An applicant is not required to amend a submitted certification in response to patent information submitted after approval of the 505(b)(2) application or ANDA (unless a patent certification is required with a supplement to the 505(b)(2) application or ANDA). 	<u>Other Amendments (§§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2))</u> <ul style="list-style-type: none"> An applicant is not required to submit a supplement to change a submitted certification in response to patent information submitted after approval of the 505(b)(2) application or ANDA (unless a patent certification is required with a supplement to the 505(b)(2) application or ANDA).

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.E.1. Amended Patent Certifications After a Finding of Infringement

We are proposing to amend §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) to reflect changes to the FD&C Act made by the MMA that clarify the requirements for a 505(b)(2) or ANDA applicant, respectively, to amend their paragraph IV certification after a judicial finding of patent infringement. As further discussed in section II.M, the MMA amended section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act to specify the types of court decisions that will terminate a 30-month stay of approval, given that many patent infringement actions previously had been concluded without a “final judgment” regarding infringement being entered by a court. With respect to a 505(b)(2) or ANDA applicant that had submitted a paragraph IV certification resulting in a patent infringement action, the FD&C Act provides that if, before the expiration of the 30-month stay of approval, the district court hearing the patent infringement action decides that the patent has been infringed and the district court’s judgment is either not appealed or is affirmed on appeal, the 505(b)(2) application or ANDA may be approved on the date specified by the district court that is not earlier than the date of expiration of the patent (including any

patent extension) and of any applicable exclusivity (see section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act and 35 U.S.C. 271(e)(4)(A)).

We are proposing to amend §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) to require that a 505(b)(2) and ANDA applicant, respectively, submit an amendment to change its paragraph IV certification to a paragraph III certification (stating that the patent will expire on a specific date) or, if appropriate, to a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act if a “court enters a final decision from which no appeal has been or can be taken” that the patent at issue has been infringed. After a final court decision of patent infringement from which no appeal has been or can be taken, a 505(b)(2) or ANDA applicant can no longer lawfully maintain a paragraph IV certification that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the 505(b)(2) application or ANDA has been submitted (see, e.g., Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1281 (D.C. Cir. 2004) (concluding that after the district court’s finding of patent validity and infringement, the ANDA applicant’s paragraph IV certification was “at variance with the legal reality” and “no longer accurate”)). These proposed revisions to §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) reflect a change to the current text requiring a 505(b)(2) or ANDA applicant to amend its paragraph IV certification if a “final judgment” has been entered finding the patent to be infringed.

Proposed §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) also would require a 505(b)(2) and ANDA applicant, respectively, to submit an amendment to change its paragraph IV certification to a paragraph III certification or, if appropriate, to a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act if a court signs a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order or consent decree also finds the patent to be invalid. For a first ANDA

applicant, submission of an amendment that changes the paragraph IV certification that qualified the applicant for 180-day exclusivity to a paragraph III certification or a statement under section 505(j)(2)(A)(viii) of the FD&C Act has implications for continuing eligibility for 180-day exclusivity (see section 505(j)(5)(D)(i)(III) of the FD&C Act). We note, however, that if a settlement is reached without a finding of patent infringement or invalidity, then a paragraph IV certification may continue to be appropriate. For example, if the 505(b)(2) or ANDA applicant is granted a patent license such that the applicant would be permitted to obtain approval and commence marketing prior to patent expiration, the 505(b)(2) or ANDA applicant would maintain its paragraph IV certification with respect to the patent at issue and should submit an amendment pursuant to proposed §§ 314.50(i)(3) and 314.94(a)(12)(v) to advise the Agency of the patent licensing agreement. Such an amendment must include a written statement by the applicant that it has been granted a patent license and a written statement from the patent owner confirming the licensing agreement and consenting to approval of the application as of a specific date (see proposed §§ 314.50(i)(3) and 314.94(a)(12)(v)).

We are proposing to apply the requirement that a 505(b)(2) or ANDA applicant must submit an amendment to change its paragraph IV certification to a paragraph III certification or, if appropriate, to a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act after a judicial finding of patent infringement irrespective of whether the patent infringement action was brought within 45 days of receipt of the notice of paragraph IV certification (see proposed §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A)). A patent infringement action initiated outside of the 45-day period following receipt of a notice of paragraph IV certification is not eligible for a 30-month stay of approval while the patent infringement litigation is pending (see § 314.107(b)(3)). However, the rationale for an amended patent certification in the event that the

patent is found valid and infringed applies with equal force to a legal action for infringement of a listed patent that was brought outside of the 45-day period (see 35 U.S.C. 271(e)(4)). Thus, we are proposing to remove the phrase “within 45 days of the receipt of notice sent under [§ 314.52 or § 314.95, respectively]” from the description of the patent infringement action to which §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) apply. This proposed revision would clarify, for example, that the approval of a 505(b)(2) application or ANDA that contained a paragraph IV certification but was not subject to a 30-month stay still may be delayed by the intervening grant of pediatric exclusivity under section 505A(b)(1)(B) of the FD&C Act after a judicial finding of infringement of the patent for which the paragraph IV certification had been submitted (see Mylan Labs., Inc. v. Thompson, 332 F. Supp. 2d 106 (D.D.C.), aff’d, 389 F.3d 1272 (D.C. Cir. 2004); see also proposed § 314.107(b)(4) and (e)(1)(vi)).

As explained in proposed §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A), an applicant may change its paragraph IV certification for a method-of-use patent to a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act only if the applicant amends its 505(b)(2) application or ANDA, respectively, such that the applicant is no longer seeking approval for a method of use claimed by the patent (see §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii)).

II.E.2. Amended Certifications After Request by the NDA Holder to Remove a Patent or Patent Information from the List

We are proposing to revise §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) to clarify the circumstances and timeframe in which a 505(b)(2) or ANDA applicant, respectively, must submit an amended patent certification to its 505(b)(2) application or ANDA after an NDA holder has requested removal of a patent or patent information from the list (“patent delisting”).

These proposed revisions also describe our current practice regarding patent delisting as it relates to the eligibility of one or more first ANDA applicants for 180-day exclusivity.

An NDA holder may request removal of a patent or patent information from the list in accordance with a court order or on its own initiative, if it determines that the patent or patent information no longer meets the statutory criteria for listing (see section 505(b)(1) and (c)(2) of the FD&C Act). Since April 18, 2008, FDA has identified in the Orange Book (the list) those patents for which an NDA holder has withdrawn the patent and submitted a request for removal of the patent from the list. We are proposing to revise §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) to state that if an NDA holder has requested removal of a patent or patent information from the list, the patent or patent information will be removed if no ANDA applicant has submitted a paragraph IV certification to the patent or no ANDA applicant is eligible for 180-day exclusivity. Upon removal of the patent or patent information from the list, any applicant with a pending 505(b)(2) application or ANDA (including a tentatively approved 505(b)(2) application or ANDA) must submit an amendment to its application to withdraw its certification to the patent.

However, if an NDA holder has requested removal of a patent or patent information from the list and one or more first ANDA applicants are eligible for 180-day exclusivity, FDA will not remove the patent or patent information from the list until we have determined that no first applicant still is eligible for 180-day exclusivity (see section 505(j)(5)(D) of the FD&C Act regarding forfeiture of 180-day exclusivity) or the 180-day exclusivity is extinguished (see proposed §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B)). Otherwise, if the NDA holder withdrew the patent or patent information for which a first ANDA applicant had submitted the certification that qualified it for 180-day exclusivity and FDA immediately removed the patent or

patent information from the list, the first applicant would be required to withdraw its patent certification and could not “lawfully maintain” its paragraph IV certification (as the ANDA would no longer be considered to be one containing a paragraph IV certification) (see section 505(j)(5)(B)(iv)(II)(bb) and (j)(5)(D)(i)(III) of the FD&C Act). In addition, if FDA immediately removed a patent or patent information from the list upon the NDA holder’s request when one or more first applicants were eligible for 180-day exclusivity, it could result in ANDA applicants withdrawing corresponding patent certifications prematurely and thus undermining a first applicant’s 180-day exclusivity. We also are proposing to revise the heading for §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) by replacing the phrase “after removal of a patent” with “after request to remove a patent or patent information” to emphasize that FDA will not remove a patent or patent information from the list until we have determined that no first applicant is eligible for 180-day exclusivity.

An NDA holder’s withdrawal of a patent or patent information is implicitly an acknowledgment that the standard for patent listing set forth in section 505(b) and (c) of the FD&C Act can no longer be met. Nevertheless, a patent for which the NDA holder has requested removal may remain listed for 180-day exclusivity purposes. For a patent that remains listed for purposes of 180-day exclusivity after an NDA holder has withdrawn the patent or patent information and requested that FDA remove the patent or patent information from the list, the requirements for providing a patent certification will differ between 505(b)(2) applicants and ANDA applicants. A 505(b)(2) applicant is neither eligible for nor blocked by 180-day generic drug exclusivity. Accordingly, we are proposing to revise § 314.50(i)(6)(ii) to exempt a 505(b)(2) applicant from the requirement to provide or maintain a certification to a patent that is identified in the Orange Book as remaining listed only for purposes of a first applicant’s 180-day

generic drug exclusivity. Because one or more ANDA applicants may be eligible for 180-day exclusivity, ANDA applicants are required to provide an appropriate patent certification to each patent listed in the Orange Book (except as provided in § 314.94(a)(12)(vi)), including to a patent that is listed with a notation indicating that the NDA holder has requested removal of the patent or patent information from the Orange Book. Once FDA has determined that no first applicant is eligible for 180-day exclusivity, or such exclusivity is extinguished, and has removed the patent information from the Orange Book, an ANDA applicant must submit an amendment to its pending ANDA to withdraw the certification.

We are proposing to delete the statement in current §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) regarding the timing of removal of a patent or patent information that is the subject of a patent infringement lawsuit under § 314.107(c). This statement would be replaced by the broader criterion, discussed earlier in this section, that a patent will not be removed from the list until FDA has determined that any 180-day exclusivity is extinguished. This proposed revision reflects our current practice.

We also are proposing to add a statement to emphasize that if a 505(b)(2) or ANDA applicant submits an amendment to withdraw a paragraph IV certification, the 505(b)(2) application or ANDA will no longer be considered to be one containing a paragraph IV certification to the patent. In addition, we are proposing a conforming revision to § 314.94(a)(12)(viii) to clarify that once an amendment is submitted to change a certification, the ANDA will no longer be considered to contain the prior certification. This is consistent with the Agency's practice for amended patent certifications for 505(b)(2) applications (see § 314.50(i)(6)).

Finally, we are proposing to relocate within §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) and revise the current statement regarding submission of an amended patent certification after removal of a patent from the list. This proposed revision is intended to clarify rather than substantively change our current requirements. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application or the RLD identified in the ANDA, the applicant must submit an amended certification under § 314.50(i)(1)(ii) or § 314.94(a)(12)(ii), as appropriate, to reflect that there are no listed patents. We note, however, that if a 505(b)(2) or ANDA applicant fails to submit an amended patent certification after removal of a patent from the list, the Agency will consider the 505(b)(2) or ANDA applicant to have constructively withdrawn its patent certification to the delisted patent (compare Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15, 21 (D.D.C.), aff'd, 2004 U.S. App. LEXIS 8311 (D.C. Cir. 2004); see also section II.E.4). With respect to any patents that remain listed for the listed drug(s) identified in the 505(b)(2) application or for the RLD identified in the ANDA, it is expected that the applicant would maintain an accurate patent certification consistent with current regulatory requirements (see §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C)). We seek comment on this approach.

II.E.3. Amended Certifications Upon Patent Reissuance

In section II.B.1.e, we describe certain proposed revisions to our regulations to clarify our requirements regarding an NDA holder's submission of patent information related to reissued patents. Because the listing of a reissued patent may require submission of an amended patent certification by a 505(b)(2) or ANDA applicant under our current regulations, we are describing in this section of the document an applicant's patent certification obligations with respect to a reissued patent.

Sections 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C) require that a 505(b)(2) and ANDA applicant submit an amended patent certification if, at any time before approval of the 505(b)(2) application or ANDA, the applicant learns that the submitted certification is no longer accurate. As a general rule, we require a 505(b)(2) or ANDA applicant to provide an appropriate patent certification or statement with respect to a reissued patent, unless either the original patent or the reissued patent was not timely filed by the NDA holder for listing in the Orange Book (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). As noted in section II.B.1.e, if a 505(b)(2) or ANDA applicant is not required to provide a patent certification or statement to the original patent because it was untimely filed (and late-listed as to the pending 505(b)(2) application or ANDA), the 505(b)(2) or ANDA applicant would not be required to provide a patent certification or statement to the reissued patent even if timely filed following reissuance.

We require a 505(b)(2) or ANDA applicant to provide an amended patent certification or statement to the reissued patent, even though a patent certification or statement may already have been submitted for the original patent, because the scope of claims may be narrowed or, in certain circumstances, broadened upon reissuance of the patent (see 35 U.S.C. 251). A change in the scope of the patent claims may result in the reissued patent being listed in the Orange Book with a revised designation by the NDA holder regarding whether the patent claims the drug substance, drug product, and/or a method of use, or the reissued patent may be listed with a revised use code. Accordingly, submission of an amendment to a pending 505(b)(2) application or ANDA is necessary to provide an appropriate patent certification or statement to the reissued patent, even if the type of patent certification (e.g., a paragraph III certification) does not differ from that submitted for the original patent.

If an ANDA applicant submitted a paragraph IV certification to the original listed patent and continues to opine that the reissued patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the application is submitted, then we are proposing that the applicant must submit an amendment to its pending ANDA that contained a paragraph IV certification to the reissued patent within 30 days of the date of listing of the reissued patent in the Orange Book to lawfully maintain its paragraph IV certification for purposes of eligibility for 180-day exclusivity (see proposed § 314.94(a)(12)(viii)(B)). Both 505(b)(2) and ANDA applicants are required to provide notice of the paragraph IV certification to the reissued patent and comply with other applicable regulatory requirements at the time of submission of the amendment containing the paragraph IV certification. We seek comment on this proposal.

An amended patent certification to the reissuance of an original patent for which a paragraph IV certification previously was submitted may have implications for the 30-month stay provisions of the FD&C Act:

- If a 505(b)(2) or ANDA applicant submitted a paragraph IV certification to the original patent and a patent infringement action was initiated within 45 days of its notice of the paragraph IV certification to the original patent, the resulting 30-month stay would not be affected solely by reissuance of the patent, recertification, and renotification and would continue subject to § 314.107.
- If a 505(b)(2) or ANDA applicant submitted a statement under section 505(b)(2)(B) or section 505(j)(2)(A)(viii) of the FD&C Act, respectively, or a paragraph III certification to the original patent and subsequently submitted a paragraph IV certification to the reissued patent, a 30-month stay would be available if a patent infringement action was

initiated within 45 days of its notice of the paragraph IV certification to the reissued patent.

- If a 505(b)(2) or ANDA applicant had previously submitted a paragraph IV certification to the original patent and no patent infringement action was initiated within 45 days of receipt of notice, no subsequent patent infringement action with respect to the reissued patent can give rise to a 30-month stay.

This approach reflects our proposal to treat the original patent and the reissued patent as a “single bundle” of patent rights, albeit patent rights that have changed with reissuance, such that the patent information listed for the reissued patent would have been submitted under 505(b)(1) or 505(c)(2) of the FD&C Act at the time of listing of the original patent for purposes of section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act. Although we recognize that a reissued patent may have a broadened scope of claims if applied for within 2 years from the grant of the original patent (see 35 U.S.C. 251), our proposal to consider the original patent and reissued patent together for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity that relates to a paragraph IV certification is intended to provide a consistent and predictable approach to implementation of the FD&C Act. If FDA were to propose a different approach to the availability of a 30-month stay based on a paragraph IV certification to a reissued patent with broadened claims, the implementation of such an approach would require resources and patent expertise that FDA currently does not possess and would be inconsistent with the Agency’s ministerial role in patent listing. In any event, we do not expect that the scenario described here will occur frequently.

An amended patent certification to the reissuance of an original patent for which a paragraph IV certification previously was submitted also may have implications for the 180-day

exclusivity provisions of the FD&C Act. As described previously in this section of the document, if a one or more first ANDA applicants is eligible for 180-day exclusivity based on a paragraph IV certification to the original patent and the patent is reissued, the first ANDA applicant would be required to submit a paragraph IV certification to the reissued patent within 30 days of listing to be considered by FDA to have lawfully maintained its paragraph IV certification for purposes of section 505(j)(5)(B)(iv)(II)(bb) and (j)(5)(D)(i)(III) of the FD&C Act. We note that the original patent, which qualified the first applicant for 180-day exclusivity, would remain listed in the Orange Book until FDA determined that any 180-day exclusivity is extinguished. Consistent with our current practice regarding requests for patent delisting, the original patent that qualified a first applicant for 180-day exclusivity also would remain listed in the Orange Book even if the scope of the reissued patent is narrowed such that the patent is no longer eligible for listing pursuant to section 505(b)(1) or 505(c)(2) of the FD&C Act and the NDA holder has requested, as required, that the patent be delisted from the Orange Book (see proposed § 314.53(f)(2) and section II.B.4.b). Given that FDA will continue to list a patent that qualified a first applicant for 180-day exclusivity under specified circumstances even if the patent has been withdrawn by the NDA holder on its own initiative or after a judicial finding of invalidity or unenforceability, the fact that the original patent technically is surrendered upon reissuance is not relevant to FDA's assessment of a first applicant's continued eligibility for 180-day exclusivity. However, in recognition of the surrender of the original patent upon reissuance, we require a first applicant to maintain a paragraph IV certification to the reissued patent. If a first applicant submitted only a paragraph III certification or a 505(j)(2)(A)(viii) statement to the reissued patent, we would consider the first applicant to have amended or withdrawn its

paragraph IV certification to the patent for which it qualified for 180-day exclusivity under section 505(j)(5)(D)(i)(III) of the FD&C Act.

If no applicant had submitted a paragraph IV certification to the original patent, the first ANDA applicant to submit a paragraph IV certification to the reissued patent could be eligible for 180-day exclusivity, if no other applicant already has qualified as a first applicant based on an earlier paragraph IV certification to another listed patent. However, if a first applicant who qualifies as such based on a paragraph IV certification to the original patent forfeits 180-day exclusivity, 180-day exclusivity would not be available to a subsequent applicant that submitted a paragraph IV certification to the reissued patent (see section 505(j)(5)(D)(iii)(II) of the FD&C Act).

II.E.4. Other Amended Certifications

Sections 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C) require a 505(b)(2) and ANDA applicant, respectively, to amend a submitted certification if, at any time before approval of the application, the applicant learns that the submitted certification is no longer accurate. In Dr. Reddy's Labs., Inc. v. Thompson, the district court held that our regulations "imposing a duty upon ANDA applicants to assure its certifications are accurate until the date of final approval is supported by [the] ... express FDA authority [in section 505(j)(4)(J) and (K) of the FD&C Act]" (302 F. Supp. 2d 340, 355 (D.N.J. 2003)) (see also section 505(e) of the FD&C Act).

Over the years, many 505(b)(2) and ANDA applicants have neglected to amend a previously submitted patent certification after the patent has expired. The Agency's longstanding position has been that a patent is relevant for purposes of 180-day exclusivity determinations "until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first" (1994 final rule, 59 FR 50338 at 50348). Section 505(j)(5)(D)(i)(VI) of

the FD&C Act, added by the MMA, is consistent with FDA's longstanding position that 180-day exclusivity is extinguished upon expiration of the patent(s) on which exclusivity is based (see Docket No. FDA-2004-N-0062-0006 (comment submitted by PhRMA) at 5, available at <http://www.regulations.gov>).

Accordingly, we are proposing to codify our longstanding position that if an applicant that previously submitted a paragraph III certification, a paragraph IV certification, or a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act with respect to a listed patent fails to amend its patent certification to a paragraph II certification upon patent expiration, the Agency will consider the 505(b)(2) or ANDA applicant to have constructively changed its patent certification to a paragraph II certification (see, e.g., Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15, 21 (D.D.C.), aff'd, 2004 U.S. App. LEXIS 8311 (D.C. Cir. 2004) (finding that upon patent expiration an ANDA applicant's paragraph IV certifications "became invalid, and either converted as a matter of law to Paragraph II certifications or became inaccurate, thereby creating both an obligation on [the ANDA applicant's] ... part to amend its ANDAs to reflect patent expiry and an inability on the part of the FDA to approve the ANDAs in their inaccurate form")). This approach also will clarify that any pediatric exclusivity will delay approval of a 505(b)(2) application or ANDA upon patent expiry under section 505A(b)(1)(B) and (c)(1)(B) of the FD&C Act, regardless of whether an applicant has amended its certification to a paragraph II certification.

We also are proposing to amend §§ 314.50(i)(6)(iii)(A) and 314.94(a)(12)(viii)(C)(1) by revising and redesignating the current text as paragraph (1) and paragraph (i), respectively, and adding a new paragraph (2) and paragraph (ii) to expressly codify the requirement for a 505(b)(2) and ANDA applicant to submit a patent certification to a newly issued patent.

Proposed §§ 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(viii)(C)(1)(ii) state that, except as provided in §§ 314.50(i)(4) and (i)(6)(iii)(B) and 314.94(a)(12)(vi) and (a)(12)(viii)(C)(2), an applicant must submit a patent certification or statement if, after submission of the 505(b)(2) application or ANDA, a new patent is issued by the PTO that, in the opinion of the applicant and to the best of its knowledge, claims the listed drug or RLD or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the FD&C Act and § 314.53.

A 505(b)(2) and ANDA applicant currently are required to submit a patent certification or statement for each patent issued by the PTO that, in the opinion of the applicant and to the best of its knowledge, claims the listed drug or RLD or that claims an approved use for such drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b) and (c) of the FD&C Act and § 314.53. Although the general requirement to submit a patent certification to a newly issued patent is established by §§ 314.50(i)(1)(i)(A) and 314.94(a)(12)(i)(A) and implicit in the exceptions for late submission of patent information, we are proposing to expressly codify the requirement to submit a patent certification to a newly issued patent in the section of the regulations directed to amended patent certification.

As discussed in section II.D.1.b.ii, we are proposing that a patent certification or statement by an ANDA applicant must not be submitted earlier than the first working day after the day the patent is published in the Orange Book (see proposed § 314.94(a)(12)(viii)(C)(1)(ii)). Thus, for a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the Orange Book. This proposal is intended to discourage burdensome serial submissions of paragraph IV certifications and ensure

that all ANDA applicants (irrespective of time zone) have a reasonable opportunity to be a first applicant with respect to a newly listed patent (see also proposed § 314.95(b)(2)).

In addition, we are proposing to revise §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C) to technically correct, but not substantively change, the reference to the lack of a requirement to “amend” a submitted patent certification after approval of a 505(b)(2) application or ANDA, respectively. We are proposing to correct this statement to indicate that an applicant is not required to submit a supplement solely to change a submitted patent certification after approval of the application. This revision also reflects that any changes to an application after approval would be made in a supplement to the application and not in an amendment, as the current regulation describes.

II.F. Patent Certification Requirements for Amendments and Supplements to 505(b)(2)

Applications and ANDAs (Proposed §§ 314.60, 314.70, 314.96, and 314.97)

We are proposing to add §§ 314.60(f), 314.70(i), 314.96(d), and 314.97(c) to clarify and augment the patent certification requirements for amendments and supplements described in §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C). Proposed §§ 314.60(f) and 314.96(d) would require an applicant to also submit a patent certification described in §§ 314.50(i) or 314.94(a)(12), as appropriate, if approval is sought for any of the following types of amendments to an original 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in product formulation; or (4) to change the physical form or crystalline structure of the active ingredient.

Currently, an applicant that submits an amendment to a pending 505(b)(2) application or supplement or a pending ANDA or supplement is required to amend its patent certification if, at any time before approval, the applicant learns that the previously submitted patent certification is

no longer accurate with respect to the pending application or supplement, as amended (see §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C), respectively, and section II.E.4). For example, an amendment to change the formulation of a proposed product in a 505(b)(2) application or ANDA would require a revised patent certification if, in the applicant's opinion and to the best of its knowledge, the new formulation would infringe a listed patent for which it previously had filed a paragraph IV certification.

Some NDA holders have expressed concern that a 505(b)(2) or ANDA applicant may change its proposed product in an amendment to a pending application, but not update its patent certification to correspond to the proposed product as changed by the amendment. For example, in 2003, FDA received a citizen petition submitted on behalf of Biovail Corporation requesting, among other things, that FDA require submission of a new patent certification upon amendment of the chemistry, manufacturing, and controls section of an ANDA (Docket No. FDA-2003-P-0519 (Biovail Petition), available at <http://www.regulations.gov>; see also PhRMA comment to Docket No. FDA-2002-N-0279-0061 at 9 to 10, available at <http://www.regulations.gov>). The Biovail Petition recognized that even if the ANDA (or 505(b)(2)) applicant continued to assert that a paragraph IV certification was the appropriate patent certification for the changed product, the factual and legal basis of the applicant's opinion that the patent will not be infringed may have changed in light of the changes in product formulation (see Biovail Petition at 4 to 5). Biovail maintained that "[r]equiring a new patent certification whenever the CMC portion of an ANDA is amended will allow the NDA holder and patent owner to ensure that the impact of the amendment on patent infringement issues is addressed promptly" (Supplement to Biovail Petition at 1).

We agree that certain changes to a proposed product submitted in a 505(b)(2) application or ANDA should be accompanied by a new patent certification (see section II.F.2). To address these concerns and further clarify our requirements for submission of new patent certifications with an amendment to a 505(b)(2) application or ANDA, we are proposing to add §§ 314.60(f) and 314.96(d). If an applicant submits an amendment to a 505(b)(2) application or ANDA for any of the categories of changes described in these provisions and does not submit a new patent certification, the applicant will be required to verify that the proposed change described in the amendment is not the type of change for which a new patent certification is required (e.g., the proposed formulation change meets the criteria for a “minor” formulation change). We seek comment on this proposal.

We also are proposing to add §§ 314.70(i) and 314.97(c), and make conforming revisions to §§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2), to clarify our requirements for submission of new patent certifications with a supplement to a 505(b)(2) application or ANDA. Proposed §§ 314.70(i) and 314.97(c) would require an applicant to also submit a patent certification described in § 314.50(i) or 314.94(a)(12), as appropriate, if approval is sought for either of the following types of supplements to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use or (2) to add a new strength.

FDA is not proposing to require a patent certification with a supplement to change the formulation or to change the physical form or crystalline structure of the active ingredient of a product approved in a 505(b)(2) application or ANDA. It is not necessary for FDA to use its limited resources to require patent certifications under these circumstances because the NDA holder for a listed drug and any patent owner can monitor postapproval changes in the formulation or active ingredient of a marketed drug product and address any patent-related

concerns without the involvement of FDA. With respect to NDA supplements, it should be noted that these patent certification requirements apply to 505(b)(2) supplements, irrespective of whether the original application to which the supplement was submitted was approved as a stand-alone 505(b)(1) application or a 505(b)(2) application. A supplement to a 505(b)(2) application of the type described in proposed § 314.70(i) is generally a 505(b)(2) supplement.

Table 10 summarizes the proposed changes related to patent certification requirements for amendments and supplements to 505(b)(2) applications and ANDAs:

Table 10.--Highlights of Proposed Changes Regarding Patent Certification Requirements for Amendments and Supplements to 505(b)(2) Applications and ANDAs¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Amended certifications—Other amendments (§§ 314.50(i)(6)(iii), 314.94(a)(12)(viii)(C))</u></p> <ul style="list-style-type: none"> Except as otherwise provided, an applicant must amend a submitted certification if, at any time before approval of the 505(b)(2) application or ANDA, the applicant learns that the submitted certification is no longer accurate. 	<p><u>Amended certifications—Other amendments (§§ 314.50(i)(6)(iii), 314.94(a)(12)(viii)(C))</u></p> <ul style="list-style-type: none"> Except as otherwise provided, an applicant must amend a submitted certification if, at any time before approval of the 505(b)(2) application or ANDA, the applicant learns that the submitted certification is no longer accurate. <p><u>Patent certification requirements (§§ 314.60(f) and 314.96(d)).</u></p> <ul style="list-style-type: none"> Except as provided below, an amendment to a 505(b)(2) application or ANDA is required to contain patent certifications described in §§ 314.50(i) or 314.94(a)(12), respectively, if approval is sought for any of the following types of amendments or supplements: <ul style="list-style-type: none"> --(1) To add a new indication or other condition of use; --(2) to add a new strength; --(3) to make other than minor changes in product formulation; or --(4) to change the physical form or crystalline structure of the active ingredient. <p><u>Patent certification requirements (§§ 314.70(i) and 314.97(c)).</u></p> <ul style="list-style-type: none"> Except as provided below, a supplement to a 505(b)(2) application or ANDA is required to contain patent certifications described in §§ 314.50(i) or 314.94(a)(12), respectively, if approval is sought for either of the following types of supplements: <ul style="list-style-type: none"> --(1) To add a new indication or other condition of use; or --(2) to add a new strength. A supplement to a 505(b)(2) application that seeks approval to add a new indication or other condition of use is required to contain patent certifications described in § 314.50(i) only for patents that are identified as claiming an approved use. If the method-of-use patent is identified as also claiming the drug substance or drug product, the patent certification also must address the drug substance and/or drug product claims.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

We invite comment on this proposal and whether a new patent certification should be required with the submission of other types of amendments or supplements to a 505(b)(2) application or ANDA that may change the drug product in a manner that could be protected by patent.

II.F.1. Types of Amendments or Supplements for Which Patent Certification is Required

II.F.1.a. Amendments or supplements to add a new indication or other condition of use.

Proposed §§ 314.60(f)(1), 314.70(i)(1)(i), 314.96(d)(1), and 314.97(c)(1) require a 505(b)(2) or ANDA applicant to submit a new patent certification with an amendment or supplement to add a new indication or other condition of use for the drug product that is the subject of the 505(b)(2) application or ANDA. Although most requests for approval of a different indication or condition of use by a 505(b)(2) applicant could not be made as an amendment to the 505(b)(2) application (see Separate Marketing Application Guidance at 4 to 5), there are certain scenarios in which an applicant may submit an amendment to a 505(b)(2) application (or ANDA) for a new indication or other condition of use. For example, a 505(b)(2) or ANDA applicant seeking approval for a drug product for which the indication has changed from prescription status to OTC use for the listed drug relied upon or RLD, as applicable, would be required to submit a new patent certification with an amendment or supplement to the application. These patent certification requirements are currently encompassed by §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C). Proposed §§ 314.60(f)(1), 314.70(i)(1)(i), 314.96(d)(1), and 314.97(c)(1) would parallel the requirements for submission of patent information by an NDA applicant seeking approval of a supplement to add a new indication or other condition of use (see proposed § 314.53(d)(2)(ii)).

Currently, an applicant is required to submit a patent certification or statement with a 505(b)(2) supplement that seeks approval for a new indication or other condition of use

(“efficacy supplement”). We are proposing to reduce the current patent certification requirements with respect to a supplement to a 505(b)(2) application that seeks approval for a new indication or other condition of use. Proposed § 314.70(i)(2) states that a supplement to a 505(b)(2) application that only seeks approval to add a new indication or other condition of use is required to contain patent certifications described in § 314.50(i) only for patents that are identified as claiming an approved use. This proposed change preserves the NDA holder’s intellectual property rights without requiring the 505(b)(2) applicant to submit a duplicative certification to patents listed in the Orange Book for the listed drug relied upon that have not been identified by the NDA holder as claiming a method of use and would not be implicated by the efficacy supplement. We note, however, that if a method-of-use patent is identified as also claiming the drug substance or drug product, a statement under section 505(b)(2)(B) of the FD&C Act would not be sufficient. The 505(b)(2) applicant’s patent certification also must address the drug substance and/or drug product claims in the patent.

II.F.1.b. Amendments or supplements to add a new strength or change an existing strength. Proposed §§ 314.60(f)(2), 314.70(i)(1)(ii), 314.96(d)(2), and 314.97(c)(2) would codify our current requirements with respect to an applicant’s submission of a new patent certification with an amendment or supplement to add a new strength for the drug product that is the subject of the 505(b)(2) application or ANDA. As noted in section II.A.2.q, it is our longstanding practice to regard different strengths of a drug product as different drug products (see Apotex, Inc. v. Shalala, 53 F. Supp. 2d 454 (D.D.C.), aff’d, 1999 U.S. App. LEXIS 29571 (D.C. Cir. 1999)).

II.F.1.c. Amendments to make other than minor changes in product formulation. Proposed §§ 314.60(f)(3) and 314.96(d)(3) would require a 505(b)(2) or ANDA applicant to

submit a new patent certification with an amendment to make other than minor changes in the formulation of the drug product that is the subject of the original 505(b)(2) application or ANDA. This enhanced patent certification requirement is intended to facilitate ongoing compliance with section 505(b)(2)(A) and (j)(2)(A)(vii) of the FD&C Act. An applicant that submits a 505(b)(2) application or ANDA containing a paragraph IV certification to a listed patent must reevaluate whether the patent certification continues to be accurate after a change to the formulation of the proposed product submitted in an amendment to the 505(b)(2) application or ANDA. By requiring a new patent certification and, with respect to a paragraph IV certification, a new notice of paragraph IV certification to be sent at the same time the amendment for the change in formulation is submitted to FDA, we aim to uphold the legislative balance of the Hatch-Waxman Amendments that facilitates the availability of generic drug products while protecting innovator intellectual property rights. We seek comment on this proposal.

This requirement would apply to all amendments to change the formulation of a proposed product in an original 505(b)(2) application or ANDA, except for minor changes in product formulation that FDA would regard as resulting in essentially the same product. A new patent certification would not be required if the new formulation in the amendment is qualitatively (Q1) the same as the previous formulation (i.e., contains all of the same inactive ingredients) and quantitatively (Q2) essentially the same (i.e., each inactive ingredient differs by no more than plus or minus 5 percent from the previous formulation). These limits correspond to the Agency's policy on products that generally can be regarded as essentially the same (see, e.g., draft guidance for industry entitled "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" (April 2003) at 8, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf>; compare § 314.70(b)(2)(i)), and thus a change within these limits would not be likely to affect an applicant's patent certification. These limits also are similar to "Level 1" changes (those that are unlikely to have any detectable impact on formulation quality and performance) in components and composition of a drug product under the Agency's Scale-Up and Postapproval Changes guidance (see guidance for industry entitled "Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (November 1995) at 6 to 8, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070636.pdf>).

It should be noted that an applicant seeking approval for an ANDA for a product intended for parenteral, ophthalmic, otic, or topical use must submit information to show that the proposed product contains the same inactive ingredients in the same concentration as the RLD, subject to exceptions specified in § 314.94(a)(9)(iii) through (a)(9)(v). Additional regulatory considerations related to changes to the formulation of a drug product proposed in an amendment to an ANDA are discussed in section II.G.1 to II.G.2 and II.L.

II.F.1.d. Amendments to change the physical form or crystalline structure of the active ingredient. Proposed §§ 314.60(f)(4) and 314.96(d)(4) would require a 505(b)(2) or ANDA applicant to submit a new patent certification with an amendment to change the physical form (e.g., different waters of hydration, solvates, and amorphous forms) or crystalline structure of the active ingredient of the drug product that is the subject of the 505(b)(2) application or ANDA. For example, a new patent certification would be required for an amendment to an ANDA that

includes a change to the physical form of the active ingredient to conform with the physical form(s) of the active ingredient described in a final USP monograph.

These patent certification requirements apply to changes to the active ingredient that may be submitted as an amendment to a 505(b)(2) application or ANDA and do not alter the Agency's policy regarding the types of different active ingredients (e.g., different salts, esters, and complexes of the same active moiety) that should be submitted in a separate application (see Separate Marketing Application Guidance; see also section II.G.3 to II.G.4). We note that the Agency has long considered different polymorphs to be the "same active ingredient" and pharmaceutical equivalents (see section 1.7 of the preface to the Orange Book (33rd Edition, 2013, at xv).

II.F.2. Requirements for Notice of Paragraph IV Certifications and Implications for 180-Day Exclusivity

There are additional regulatory considerations related to the submission of a paragraph IV certification by an applicant required to submit a new patent certification with its amendment or supplement to a 505(b)(2) application or ANDA. As a preliminary matter, we note that notice is required for all paragraph IV certifications, irrespective of whether the applicant previously provided notice of paragraph IV certification to the same patent or to another patent claiming the listed drug relied upon or RLD (see section 505(b)(3)(B) and (j)(2)(B)(ii) of the FD&C Act). If patent infringement litigation has been initiated in response to a previous notice of paragraph IV certification, a new paragraph IV certification submitted with an amendment or supplement to the 505(b)(2) application or ANDA still requires formal notice in accordance with §§ 314.52 and 314.95.

The new notice of paragraph IV certification must contain the information required by section 505(b)(3)(D) and (j)(2)(B)(iv) of the FD&C Act and §§ 314.52(c) and 314.95(c), updated to correspond to the proposed product as changed by the amendment or supplement. For example, the detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed by its proposed product must be updated, as necessary, by the 505(b)(2) or ANDA applicant to reflect the changes proposed in the amendment or supplement. The notice of paragraph IV certification also must clarify whether the amendment or supplement contains any required bioavailability or bioequivalence data that was necessary to support the proposed change to the 505(b)(2) application or ANDA.

With respect to any listed patent challenged by the applicant in an amendment or supplement to the 505(b)(2) application or ANDA for which the NDA holder or patent owner initiated patent infringement litigation within the statutory timeframe in response to notice of paragraph IV certification, the availability of a 30-month stay will depend upon whether the NDA holder filed information on the patent at issue with FDA prior to the date of submission of the 505(b)(2) application or the date of submission of the ANDA (which FDA later determined to be substantially complete) that refers to the listed drug claimed by the patent (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act). Accordingly, a 30-month stay may result from initiation of a patent infringement action in response to a second notice of paragraph IV certification provided at the time of submission of an amendment or supplement to a 505(b)(2) application or ANDA if the patent was listed prior to the date of submission of the original 505(b)(2) application or ANDA and, for example, the infringement action was warranted by the change proposed in the amendment or supplement.

A first applicant that submits an amendment to its pending ANDA or a supplement would be considered to have lawfully maintained a paragraph IV certification to the patent upon which eligibility for 180-day exclusivity was based if the amendment or supplement is accompanied by another paragraph IV certification to the patent and notice of paragraph IV certification is sent in accordance with § 314.95(d).

II.G. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and
Amendments or Supplements to an ANDA That Reference a Different Listed Drug (Proposed
§§ 314.60, 314.70, 314.96, 314.97)

The MMA added section 505(b)(4)(A), (b)(4)(B), (j)(2)(D)(i), and (j)(2)(D)(ii) to the FD&C Act, which generally prohibit the submission of certain types of changes in an amendment or a supplement to a 505(b)(2) application or an ANDA, respectively. We interpret these provisions in the context of the MMA's amendment of section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act to restrict the availability of a 30-month stay of approval in certain circumstances involving amendments and supplements to a 505(b)(2) application or ANDA and seek comment on this approach.

Section 1101(a)(1)(A) of the MMA amended section 505(j) of the FD&C Act to generally prohibit an ANDA applicant from amending or supplementing an ANDA “to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted [to FDA]” (section 505(j)(2)(D)(i) of the FD&C Act). The textual reference in the statute to “seek approval of a drug referring to a different listed drug” is clearly understood in the context of section 505(j) of the FD&C Act and FDA's regulatory scheme for the approval of ANDAs. An applicant that submits an ANDA for a duplicate of a listed drug is required to identify and rely upon the listed drug designated by FDA as the RLD (see

§ 314.94(a)(3)). An applicant also may petition FDA to request permission to submit an ANDA that differs from a selected listed drug in route of administration, dosage form, or strength, or that has one different active ingredient in a combination drug product (see section 505(j)(2)(C) of the FD&C Act). Accordingly, we are proposing to add §§ 314.96(c) and 314.97(b) to state that an ANDA applicant may not amend or supplement an ANDA to seek approval of a drug referring to listed drug that is different from the RLD identified in the ANDA. An ANDA applicant that seeks to refer to a listed drug different from the RLD identified in the initial ANDA must submit a new ANDA (see section 505(j)(2)(D)(i) of the FD&C Act; see also section II.G.1 to II.G.2 of this document).

Section 1101(b)(1)(A) of the MMA amended section 505(b) of the FD&C Act to generally prohibit an applicant from amending or supplementing “an application referred to in [section 505(b)(2)] to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.” Although section 1101(a) and (b) of the MMA are parallel in structure, the statutory text restricting an applicant from amending or supplementing a 505(b)(2) application in certain circumstances differs from the corresponding restrictions for ANDAs. Section 505(b)(4)(A) prohibits an amendment or a supplement “to seek approval of a drug that is a different drug” (emphasis added) while section 505(j)(2)(D)(i) prohibits an amendment or supplement to an ANDA “to seek approval of a drug referring to a different listed drug” (emphasis added).

The MMA also amended section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act to permit a 30-month stay of approval of a 505(b)(2) application or ANDA only with respect to patents for which the NDA holder submitted information to FDA prior to the date of submission of the 505(b)(2) application or the date of submission of the ANDA (which FDA later

determines to be substantially complete) that refers to the listed drug claimed by the patent. The “date on which the application ... was submitted” specifically excludes the date of submission of an amendment or supplement to a 505(b)(2) application or ANDA. Given this limitation on the patents that may give rise to a 30-month stay, the MMA may have created an incentive for a 505(b)(2) or ANDA applicant to seek approval for a change to a drug, or to reference a different listed drug, through an amendment or a supplement, rather than by submitting a new application. To address this concern, section 505(b)(4)(A) and (j)(2)(D)(i) of the FD&C Act ensure that 505(b)(2) and ANDA applicants do not use the amendment or supplement process to evade the possibility of a 30-month stay of approval that otherwise would have applied if the 505(b)(2) applicant sought approval for a drug that is a different drug or if the ANDA applicant sought to refer to a different RLD in the original 505(b)(2) application or ANDA, respectively.

Accordingly, we interpret section 505(b)(4)(A) of the FD&C Act in a manner that is consistent with the statutory text, accomplishes the statutory goal of preserving a meaningful opportunity for a single 30-month stay, and reflects, to the extent feasible, Congress’ expressed intent to preserve rather than disrupt FDA processes regarding submission of amendments and supplements to 505(b)(2) applications and ANDAs.

We propose that a drug will be considered a “different drug” for purposes of section 505(b)(4)(A) of the FD&C Act if it has been modified to have a different active ingredient, different route of administration, or different dosage form. Similarly, a drug will be considered to be a different drug if it has been modified to have different excipients that require either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence (see proposed §§ 314.60(e) and 314.70(h)). Consistent with FDA’s “bundling” policy in effect at the time of enactment of the MMA, an

applicant may not seek approval for these types of changes to a drug through an amendment or supplement to the 505(b)(2) application; the applicant is required to submit a new 505(b)(2) application (see draft guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees” (describing FDA’s bundling policy at the time of enactment of the MMA in 2003); see also Separate Marketing Applications Guidance). These changes to a drug product are significant enough that it is reasonable to assume that one or more patents for the listed drug might be implicated by the change and, if an action for patent infringement is brought in response to a paragraph IV certification to a listed patent, an opportunity for 30-month stay would be appropriate. Thus, FDA has concluded that these modifications to a drug would make the drug a “different drug” for purposes of section 505(b)(4)(A) of the FD&C Act. An applicant seeking marketing approval for a drug that has been modified in these ways must submit a separate marketing application for the different drug product, and not an amendment or supplement.

We considered possible alternative interpretations of the phrase “to seek approval of a drug that is a different drug” in section 505(b)(4)(A) of the FD&C Act. The narrowest reading of this text would preclude the submission of an amendment or a supplement to a 505(b)(2) application for any change (including labeling changes and manufacturing changes) that would arguably render the proposed product a “different drug” than the drug identified in the original submission of the application. If labeling changes, for example, could not be made through an amendment or a supplement to a 505(b)(2) application, each such change would require the submission of a separate 505(b)(2) application, with related regulatory and administrative burdens, and user fee and review cycle implications. We did not adopt this reading because it

would have resulted in an unwarranted departure from FDA's previous practice for handling such changes.

In applying section 505(b)(4)(A) of the FD&C Act, we initially interpreted the phrase "drug that is a different drug" in section 505(b)(4)(A) in a manner that was influenced by and intended to be consistent with the phrase "drug referring to a different listed drug" in section 505(j)(2)(D)(i) of the FD&C Act. Under this interpretation, an applicant was not permitted to amend or supplement a 505(b)(2) application to seek approval of a drug that relied on the Agency's finding of safety and/or effectiveness for a listed drug that was different from the listed drug(s) identified in the original submission of the application. This approach assumed that the difference in phrasing between section 505(b)(4)(A) and (j)(2)(D)(i) of the FD&C Act was simply intended to reflect the different statutory frameworks for 505(b)(2) applications and ANDAs. This interpretation also was intended to ensure that a 505(b)(2) applicant did not circumvent the 30-month stay provisions of the FD&C Act by amending or supplementing a 505(b)(2) application to identify a new or additional listed drug upon which it relied for approval.

We found our initial approach to be overly restrictive in practice, however, as this interpretation required withdrawal and resubmission of a 505(b)(2) application to identify a new or additional listed drug even where there were no patents listed in the Orange Book for the new or additional listed drug, and thus there was no possibility of a 30-month stay.

Accordingly, we are proposing a narrower interpretation that is guided by Congress' expressed view that these provisions are intended to "reflect the FDA's current practice regarding those changes and variations to both innovator and generic drugs that may be approved

under amendments and supplements to previously filed NDAs and ANDAs ...” (see Conference Report on H.R. 1, November 20, 2003, at H12099).

Our interpretation of section 505(b)(4)(A), (b)(4)(B), (j)(2)(D)(i), and (j)(2)(D)(ii) of the FD&C Act seeks to preserve the legislative balance of the Hatch-Waxman Amendments with respect to facilitating the availability of drug products that meet the statutory requirements for approval while protecting innovator intellectual property rights (and allowing for an early resolution of any patent infringement litigation). We seek comment on this proposal and potential alternatives to maintain the intended balance.

In the Federal Register of November 4, 2004 (69 FR 64314), FDA announced the availability of a draft guidance for industry, issued as required by section 505(j)(2)(D)(iii) of the FD&C Act, that defined the term “listed drug” for purposes of section 505(j)(2)(D) with respect to amendments and supplements to an ANDA (see draft guidance for industry entitled “Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003” (October 2004), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072887.pdf>) (Draft Guidance on Listed Drugs). In the Draft Guidance on Listed Drugs, we advised that our definition of the term “listed drug” is set forth in § 314.3, and that we did not intend to amend that definition to implement section 505(j)(2)(D) of the FD&C Act. Although minor revisions to the definition of listed drug are proposed in this rulemaking (see section II.A.2.s), these proposed revisions do not substantively alter the definition for purposes of section 505(j)(2)(D) of the FD&C Act. We note that different strengths of an approved drug product continue to be regarded as different listed drugs. However, the FD&C Act expressly

permits an applicant to amend or supplement a 505(b)(2) application or ANDA to seek approval of a different strength (see section 505(b)(4)(B) and (j)(2)(D)(ii) of the FD&C Act).

Table 11 summarizes the proposed changes related to amendments or supplements to a 505(b)(2) application or ANDA:

Table 11.--Highlights of Proposed Changes Regarding Amendments or Supplements to a 505(b)(2) Application or ANDA¹

Current Regulations	Proposed Revisions to Regulations
[No corresponding regulation]	<p><u>Amendments and Supplements--Different drug (§§ 314.60(e) and 314.70(h))</u></p> <ul style="list-style-type: none"> • Applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. • Applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application. • For purposes of this section, a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. • Approval of a different drug must be requested in a new 505(b)(2) application. • Notwithstanding the limitations described above, an applicant may amend or supplement the 505(b)(2) application to seek approval of a different strength.
[No corresponding regulation]	<p><u>Amendments and Supplements--Different listed drug (§§ 314.96(c) and 314.97(b))</u></p> <ul style="list-style-type: none"> • Applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA. <ul style="list-style-type: none"> -- Applies if, at any time before ANDA approval, a different listed drug approved in an NDA is pharmaceutically equivalent to the product in the ANDA and is designated as an RLD. -- Applies if changes are proposed in an amendment to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the RLD identified in the ANDA. • Applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current RLD identified in the ANDA. <ul style="list-style-type: none"> -- Applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the RLD identified in the ANDA. • A change of the RLD must be submitted in a new ANDA. • Notwithstanding the limitations described above, an applicant may amend or supplement the ANDA to seek approval of a different strength.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.G.1. Amendments to an Unapproved ANDA (Proposed § 314.96(c))

We are proposing to revise § 314.96 regarding amendments to an unapproved ANDA by adding paragraph (c) to implement section 505(j)(2)(D)(i) and (ii) of the FD&C Act. Proposed § 314.96(c) states that an applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA. Two examples in proposed § 314.96(c) illustrate the application of this provision.

II.G.1.a. Approval of a pharmaceutically equivalent drug product. Proposed § 314.96(c) states that if at any time before approval of the ANDA, an NDA is approved for a drug product that is pharmaceutically equivalent to the product in the pending ANDA and that NDA is designated as an RLD, the applicant is not permitted to amend its pending ANDA to reference the new RLD. This change must be submitted in a new ANDA. As a preliminary matter, we note that the drug product designated as an RLD may not necessarily be the drug product identified in the Orange Book as the reference standard for bioequivalence studies, for example, for drug product lines with multiple strengths. An ANDA would not be ineligible for approval because it relied upon an RLD that was not the reference standard or because it relied upon one of two or more potential RLDs for a pharmaceutically equivalent product. FDA's policy on designating an additional RLD for multiple source products is set forth in the preamble to the 1992 final rule and also described in the preface to the Orange Book. In the 1992 final rule, we stated in relevant part: "FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA" (57 FR 17950 at 17958; see also Letter to Robert W. Pollock, Lachman Consultant Services, Inc., dated April 18,

2005, regarding Docket No. FDA-2004-P-0466 (requesting designation of DiaBeta as a second RLD for glyburide tablets, 5 mg), available at <http://www.regulations.gov>).

The scenario described in proposed § 314.96(c) arises, for example, when an ANDA is submitted after the grant of a suitability petition pursuant to section 505(j)(2)(C) of the FD&C Act for a new dosage form, route of administration, or new active ingredient (in a drug product containing more than one active ingredient) and another applicant obtains approval of an NDA (including a 505(b)(2) application) for the change described in the suitability petition before the ANDA is approved. Under these circumstances, it is FDA's longstanding position that an ANDA (including a tentatively approved ANDA) can no longer reference the approved suitability petition and the listed drug described therein as the basis for ANDA submission (see §§ 314.94(a)(3) and 314.127(a)(5), (a)(6), and (a)(12) and section II.I). Prior to enactment of the MMA, an applicant with a pending ANDA based upon an approved "suitability petition" (a petitioned ANDA) could have amended its ANDA to change the basis for submission (see § 314.94(a)(3)) to a pharmaceutically equivalent product that subsequently had been approved in an NDA and was designated by FDA as the RLD. However, the plain language of section 505(j)(2)(D)(i) of the FD&C Act (added by the MMA) prohibits an ANDA applicant from amending its ANDA to change the basis for submission to a pharmaceutically equivalent product subsequently approved in an NDA. Accordingly, for an ANDA applicant to obtain approval for a pharmaceutically equivalent product, the applicant would be required to submit a new ANDA that identifies the pharmaceutically equivalent product as its basis for ANDA submission under § 314.94 and meet applicable statutory and regulatory requirements (see, generally, discussion in the Letter from Janet Woodcock, M.D., Director, CDER, to Mark S. Aikman, Pharm.D.,

Osmotica Pharmaceutical Corp., dated November 25, 2008, regarding Docket No. FDA-2008-P-0329, available at <http://www.regulations.gov>) (Venlafaxine ER Citizen Petition Response).

FDA's policy is scientifically justified because an NDA (either a "stand-alone" NDA or 505(b)(2) application) approved for the change described in a suitability petition need not be bioequivalent to the listed drug identified in the suitability petition. For example, a 505(b)(2) applicant may develop a different dosage form of a drug product that is intentionally more bioavailable than a previously approved product (see § 314.54(b)). A 505(b)(2) applicant also may have relied upon a different listed drug in support of its 505(b)(2) application than the listed drug identified in the suitability petition. By ensuring that an ANDA has clearly demonstrated bioequivalence to a pharmaceutically equivalent drug product identified as the RLD, we enhance the utility and accuracy of FDA's therapeutic equivalence determinations. We previously have explained that "this approach reduces the potentially confusing proliferation of pharmaceutically equivalent drug products that have not demonstrated therapeutic equivalence, and ensures that ANDAs ... will be therapeutically equivalent and thus substitutable for the RLD" (Venlafaxine ER Citizen Petition Response at 13).

FDA's requirement that an applicant with a pending ANDA must change its basis for ANDA submission upon approval of an NDA for the same drug product described in the suitability petition also is intended to ensure that ANDA applicants do not circumvent the patent certification requirements of section 505(j)(2)(A)(vii) and (j)(2)(A)(viii) of the FD&C Act through the suitability petition process. Otherwise, if a patent were listed for a drug product approved in an NDA and designated as the RLD and a pending ANDA submitted pursuant to an approved suitability petition were permitted to amend its application to refer to the new RLD, even a single 30-month stay would not be available should the NDA holder or patent owner

initiate patent infringement litigation within the statutory timeframe in response to a paragraph IV certification for a patent listed after submission of the original ANDA that FDA later determined to be substantially complete. In addition, our policy appropriately protects any marketing exclusivity that has been granted to the newly approved RLD.

The Agency has rejected the argument that a pending ANDA submitted pursuant to an approved suitability petition may continue to reference the listed drug identified in the suitability petition after a pharmaceutically equivalent product has been approved in an NDA (including a 505(b)(2) application) and is designated as the RLD (see generally Venlafaxine ER Citizen Petition Response). This “reflects the Agency’s judgment that considerations regarding an ANDA’s limited reliance on an approved suitability petition are outweighed by the need for a clear determination of therapeutic equivalence for a generic drug product and protection of intellectual property rights accorded an NDA holder” (Venlafaxine ER Citizen Petition Response at 9). In section II.I, we describe our proposed revisions to § 314.93(e) and (f) to codify FDA’s policy that the listed drug identified in an approved suitability petition can no longer be the basis for submission for an unapproved ANDA after a drug product is approved in an NDA for the change described in the petition.

In the case of a first applicant that had been eligible for 180-day exclusivity based on a paragraph IV certification to a patent listed in the Orange Book for the listed drug described in the suitability petition, we note that a new assessment of first applicant status would begin upon submission of a new ANDA. This reflects the fact that any ANDA that referenced the listed drug identified in the suitability petition after approval of a pharmaceutically equivalent product could not be approved. Further, an applicant that withdrew its ANDA would not have lawfully

maintained its paragraph IV certification and would no longer be eligible for first applicant status.

II.G.1.b. Changes to the drug product proposed in the ANDA. The second example in proposed § 314.96(c) that illustrates the application of this provision involves one or more changes proposed in an amendment to an ANDA that would result in the proposed product being a pharmaceutical equivalent to a different listed drug than the RLD identified in the ANDA. This type of change must be submitted in a new ANDA that identifies the pharmaceutically equivalent product as the new RLD. In the Draft Guidance on Listed Drugs, we explained that “[a]ll changes that would have the effect of seeking approval for a drug product different from the listed drug cited in the initial submission (e.g., different active ingredient, dosage form, route of administration) should be made in a new application. When the Orange Book identifies as a separate listed drug a product with the characteristics (e.g., active ingredient, dosage form, route of administration) for which the applicant is seeking approval, the applicant should submit a separate ANDA referencing the corresponding listed drug” (Draft Guidance on Listed Drugs, at 3). This generally conforms with Agency practice before passage of the MMA with respect to certain types of changes (e.g., a change in the dosage form or a change in the formulation that may significantly affect absorption of the active drug ingredient or active moiety) that should be submitted as a separate ANDA (see guidance for industry entitled “Variations in Drug Products that May Be Included in a Single ANDA” (December 1998), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072892.pdf>) (Guidance on Drug Product Variations). For example, we noted “[g]enerally, when there is a separate NDA as a RLD for a specific drug product there should be a separate abbreviated application for that NDA” (Guidance on Drug Product Variations, at 2).

Proposed § 314.96(c) clarifies that, notwithstanding these restrictions on amendments to an ANDA, an applicant is permitted to amend an ANDA to seek approval for a different strength of the drug product (see section 505(j)(2)(D)(ii) of the FD&C Act). As discussed in section II.A.2.bb, we interpret this exception for different strengths of the drug product to include changes to the concentration or to the total drug content of a parenteral drug product. We note that, unlike original ANDAs, not all amendments are subject to a filing review by the Office of Generic Drugs to determine whether the submission may be formally received for substantive review. Accordingly, it is possible that an ANDA applicant that submits an amendment not permitted by statute may be informed late in the review process that the proposed change to its ANDA must be submitted as a new ANDA. We encourage ANDA applicants with questions about whether a proposed amendment to an ANDA would be precluded by section 505(j)(2)(D)(i) of the FD&C Act to contact the Office of Generic Drugs for further guidance.

II.G.2. Supplements to an ANDA (Proposed § 314.97(b))

We are proposing to revise § 314.97 regarding supplements by designating the current text as paragraph (a) and by adding proposed paragraph (b) to implement section 505(j)(2)(D)(i) and (ii) of the FD&C Act. Proposed § 314.97(b) explains that an applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current RLD identified in the ANDA. This restriction applies if changes are proposed in a supplement to the ANDA that would result in the proposed product being pharmaceutically equivalent to a different listed drug than the RLD identified in the underlying ANDA. This type of change must be submitted in a new ANDA that identifies the pharmaceutically equivalent product as the new RLD.

There are several types of changes that may be proposed in a supplement to an ANDA that would result in the proposed product being pharmaceutically equivalent to a different listed drug than the RLD identified in the underlying ANDA. For example, the scenario described in proposed § 314.97(b) may arise if the RLD for the drug product approved in an ANDA is subsequently changed from prescription use to OTC status for some or all conditions of use of the drug product. An ANDA holder for the drug product with the “switched” conditions of use would be required to seek approval of the drug product for OTC use because the FD&C Act does not permit a drug product to be marketed as prescription and OTC for the same conditions of use at the same time (see section 503(b) of the FD&C Act (21 U.S.C. 353(b)). However, if the NDA holder for the RLD obtained approval of the switch from prescription use to OTC status in a separate NDA (for example, if fewer than all conditions of use were switched to OTC status), then the NDA for OTC use would be considered a different RLD. Section 505(j)(2)(D)(i) of the FD&C Act does not permit an ANDA holder to refer to a different RLD in a supplement (or, with respect to a pending ANDA, an amendment) to its ANDA. This type of change must be submitted in a new ANDA that identifies the different NDA for OTC use as the RLD.

We note, however, that an ANDA holder may submit a supplement that seeks to demonstrate bioequivalence to a different listed drug when there are multiple RLDs (see, e.g., Orange Book, 33rd Edition (2013) at xx to xxi (Description of Special Situations--levothyroxine sodium)). In this case, the submission of additional bioequivalence data in an ANDA supplement is not for the purpose of seeking approval of a drug referring to a different RLD, but rather to obtain an additional therapeutic equivalence rating. This type of change may continue to be submitted as a supplement to an ANDA.

Proposed § 314.97(b) clarifies that, notwithstanding these restrictions on supplements to an ANDA, an applicant is permitted to supplement an ANDA to seek approval for a different strength of the drug product (see section 505(j)(2)(D)(ii) of the FD&C Act). As discussed in section II.G.1.b, we interpret this exception for different strengths of the drug product to include changes to the concentration or to the total drug content of a parenteral drug product (see also section II.A.2.bb).

II.G.3. Amendments to an Unapproved 505(b)(2) Application (Proposed § 314.60(e))

We are proposing to revise § 314.60 regarding amendments to an unapproved 505(b)(2) application by adding proposed paragraph (e) to implement section 505(b)(4)(A) and (b)(4)(B) of the FD&C Act. Proposed § 314.60(e) states that an applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of this section, a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence.

II.G.3.a. Applications within the scope of section 505(b)(4)(A) of the FD&C Act.

Section 505(b)(4)(A) of the FD&C Act restricts certain types of amendments and supplements to a 505(b)(2) application. We interpret this statutory provision to apply to an NDA that was submitted as a 505(b)(2) application and to an NDA that was submitted as a stand-alone 505(b)(1) application but was misclassified by the applicant. A stand-alone 505(b)(1) application would be misclassified if, for example, the application relied, at least in part, on the Agency's finding of safety and/or effectiveness for one or more listed drugs or published

literature. Such an NDA is considered to be a 505(b)(2) application even if the applicant failed to identify the listed drug(s) in accordance with § 314.54(a)(1)(iii) and comply with applicable regulatory requirements. It would be inconsistent with the statutory scheme, as amended by the MMA, to permit an applicant to circumvent the restrictions on amendments to a 505(b)(2) application and the potential implications for the availability of a 30-month stay of approval pursuant to section 505(c)(3)(C) of the FD&C Act merely by incorrectly characterizing the original submission as a stand-alone 505(b)(1) application.

We note, however, that reliance on a listed drug pursuant to section 505(b)(2) of the FD&C Act generally assumes that the drug the applicant is referencing is one for which it is not the application holder and for which it would not have a right of reference or use. Accordingly, an applicant that cross-references relevant studies in its own previous 505(b)(2) application (i.e., studies that were conducted by or for the applicant or to which the applicant has obtained a right of reference or use) would not be a 505(b)(2) applicant as to those portions of its previous 505(b)(2) application. However, an applicant may be relying, in part, for approval of its current NDA upon the Agency's finding of safety and/or effectiveness for a listed drug identified in its previous 505(b)(2) application, to which it does not have a right of reference or use. In this scenario, if an applicant continues to rely upon the original listed drug for approval of its current NDA, then it is a 505(b)(2) application and the applicant must identify the original listed drug in accordance with § 314.54 and comply with other applicable regulatory requirements.

An applicant also may not amend a literature-based 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate

clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence.

II.G.3.b. Proposed amendments subject to section 505(b)(4)(A) of the FD&C Act.

Proposed § 314.60(e) provides that the statutory restriction on amending a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application applies to any proposed amendment, even if the amendment is submitted prior to the Agency's decision regarding whether the 505(b)(2) application can be filed in accordance with § 314.101(a). This standard is consistent with the MMA's amendments to section 505(c)(3)(C) of the FD&C Act to limit the availability of a 30-month stay of approval to patents for which the NDA holder submitted information to FDA "before the date on which the application (excluding an amendment or supplement to the application) was submitted."

Under proposed § 314.60, an applicant cannot amend a 505(b)(2) application to seek approval for a drug that has been modified to have a different active ingredient. This includes, but is not limited to, a different salt, ester, or complex of the same active moiety (compare section II.F.1.d). A change in the route of administration or dosage form also cannot be made in an amendment to a 505(b)(2) application unless the product is qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the proposed drug product in the original 505(b)(2) application for all routes of administration or dosage forms, as applicable.

An applicant also cannot amend a 505(b)(2) application to seek approval for a drug that has been modified to have a difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence (see § 320.24(b)(4)). These proposed modifications would result in a different drug for which approval must be requested in a new 505(b)(2) application.

However, notwithstanding these restrictions on amendments to a 505(b)(2) application, an applicant is permitted to amend a 505(b)(2) application to identify a new or additional listed drug upon which the application relies for approval.

In addition, proposed § 314.60(e) clarifies that an applicant is permitted to amend a 505(b)(2) application to seek approval for a different strength of the drug product (see section 505(b)(4)(B) of the FD&C Act; see also sections II.A.2.bb and II.G.1.b of this document).

II.G.4. Supplements to a 505(b)(2) Application (Proposed § 314.70(h))

We are proposing to revise § 314.70 regarding supplements to an approved 505(b)(2) application by adding proposed paragraph (h) to implement section 505(b)(4)(A) and (b)(4)(B) of the FD&C Act. Proposed § 314.70(h) states that an applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of this section, a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence (see discussion in section II.G.3.b). These proposed modifications would result in a different drug for which approval must be requested in a new 505(b)(2) application.

In addition, proposed § 314.70(h) clarifies that, notwithstanding these restrictions on supplements to a 505(b)(2) application, an applicant is permitted to supplement a 505(b)(2) application to seek approval for a different strength of the drug product (see section 505(b)(4)(B) of the FD&C Act; see also sections II.A.2.bb and II.G.1.b of this document).

We interpret section 505(b)(4)(A) of the FD&C Act to apply to the submission of a 505(b)(2) supplement to an NDA approved through the 505(b)(2) pathway, irrespective of whether the original 505(b)(2) application relied upon published literature or the Agency's finding of safety and/or effectiveness for one or more listed drugs. However, because the statutory text expressly applies to a supplement to a 505(b)(2) application, we do not interpret the restriction in section 505(b)(4)(A) to apply to a 505(b)(2) supplement to an NDA that received approval as a stand-alone 505(b)(1) application unless an intervening 505(b)(2) supplement has been approved for that NDA (see § 314.3(b) (defining the term "application" to include all supplements to the application)).

II.H. Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug (Proposed § 314.54)

We are proposing to revise §§ 314.50(i), 314.54(a), and 314.125(b) to establish the requirement that an applicant identify a pharmaceutically equivalent product, if already approved, as a listed drug relied upon to support approval of a 505(b)(2) application.

FDA's longstanding policy has been that a 505(b)(2) applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness. The 505(b)(2) approval pathway is not intended for a "duplicate" of a listed drug that is eligible for approval in an ANDA, and FDA would refuse to file such a 505(b)(2) application (see § 314.101(d)(9)). The Hatch-Waxman

Amendments established a specific abbreviated approval pathway for duplicates of a listed drug in section 505(j) of the FD&C Act.

However, there are circumstances in which a proposed drug product that is pharmaceutically equivalent to a listed drug (i.e., drug products in the same dosage form and route(s) of administration that contain the same amount of the same active drug ingredient and that meet other applicable standards) is not eligible for approval as an ANDA and must be submitted as an NDA. For example, a proposed extended-release drug product may intentionally differ in its pharmacokinetic profile from a listed drug that is also an extended-release drug product such that the proposed product cannot meet the bioequivalence requirement for ANDAs (see section 505(j)(2)(A)(iv) of the FD&C Act; compare § 314.54(b)). Certain drug products intended for parenteral, ophthalmic, otic, or topical use may contain differences in excipients that render the drug product ineligible for submission in an ANDA (see § 314.94(a)(9)(iii) to (a)(9)(v)). For certain complex drug products, an applicant may be unable to demonstrate “sameness” of the active ingredient as required for submission of an ANDA (see section 505(j)(2)(A)(ii) of the FD&C Act). A request for approval of a new indication for a pharmaceutically equivalent drug product also is ineligible for submission as an ANDA. These changes to a listed drug must be submitted in an NDA.

We have explained that a 505(b)(2) applicant may rely on FDA’s finding of safety and effectiveness for a listed drug “only to the extent that such reliance would be allowed under section 505(j) of the act” (1989 proposed rule, 54 FR 28872 at 28892). If a pharmaceutically equivalent drug product has been approved before a 505(b)(2) application is submitted, then we consider the 505(b)(2) applicant to be implicitly relying on the approval of such drug product. We are proposing to revise § 314.54(a)(1)(iii) to require that the listed drug or drugs identified as

relied upon by a 505(b)(2) applicant must include any approved drug product that: (1) Is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted and (2) was approved before the 505(b)(2) application was submitted. This requirement is intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory obligation that would have applied if the proposed product was submitted as an ANDA--namely, submission of a patent certification for a listed patent that corresponds to the protected aspects of the pharmaceutically equivalent listed drug (see draft guidance for industry entitled “Applications Covered by Section 505(b)(2)” (October 1999), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>) (“If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug”). Clarifying revisions in proposed § 314.54(a)(1)(iii) and (a)(1)(vi) replace the reference to “other drugs” with “listed drug” to conform with our longstanding policy that an applicant may rely upon more than one listed drug to support approval of a 505(b)(2) application. In addition, we are proposing to replace the term “reference listed drug” in § 314.54(b) with “listed drug” because the descriptor “reference listed drug” is a term of art that applies to an ANDA. A 505(b)(2) application may rely on FDA’s finding of safety and/or effectiveness for one or more listed drugs.

We also are proposing to add § 314.50(i)(1)(i)(C) to require that if, before the date of submission of the 505(b)(2) application, there is an approved drug product that is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted, the applicant must submit an appropriate patent certification under § 314.50(i) with respect to

each patent listed for the pharmaceutically equivalent product that claims the drug substance or drug product or that claims an approved use for such drug.

We are proposing a conforming revision to § 314.125(b) to state that we may refuse to approve a 505(b)(2) application based on the applicant's failure to submit an appropriate patent certification or statement with respect to each listed patent for a drug product that: (1) Is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted and (2) was approved before the 505(b)(2) application was submitted. If FDA approves a pharmaceutically equivalent product within the 60-day filing review period after a 505(b)(2) application is submitted, the 505(b)(2) applicant is not required to identify the product as a listed drug relied upon or submit a patent certification under § 314.50(i) and FDA would not refuse to file the application under § 314.101(d)(9) based on the new approval.

It also should be noted that the requirement to identify a pharmaceutically equivalent product as a listed drug relied upon (and to submit an appropriate patent certification or statement with respect to each listed patent) does not apply if a pharmaceutically equivalent product is approved while the 505(b)(2) application is pending.

We intend to promptly publish on FDA's Web site information regarding the approval of new drug products to facilitate, among other things, a 505(b)(2) applicant's compliance with proposed § 314.54(a)(1)(iii) and (a)(1)(vi) and § 314.50(i)(1)(i)(C).

II.I. Petition to Request a Change From a Listed Drug (Proposed § 314.93)

We are proposing to amend § 314.93 regarding petitioned ANDAs to codify FDA's policy that the listed drug identified in an approved suitability petition can no longer be the basis for submission for an unapproved ANDA after a drug product is approved in an NDA for the change described in the petition (see generally Venlafaxine ER Citizen Petition Response). This

proposed revision is intended to facilitate implementation of section 505(j)(2)(D)(i) and (ii) of the FD&C Act and complement proposed revisions to § 314.96(c) regarding amendments to an unapproved ANDA (see section II.F.1.a).

We are proposing to revise § 314.93(f) regarding withdrawal of approval of a suitability petition by redesignating the current text as paragraph (f)(1) and by adding paragraph (f)(2). Proposed § 314.93(f)(2) clarifies that if, after approval of a petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the petition and the listed drug identified in the petition can no longer be the basis for ANDA submission, irrespective of whether FDA has withdrawn approval of the petition. Because an ANDA applicant may not amend its ANDA to change the basis for submission to the new RLD (see section 505(j)(2)(D)(i) of the FD&C Act), a person seeking approval for such drug product would be required to submit a new ANDA that identifies the pharmaceutically equivalent RLD as the basis for ANDA submission and comply with applicable statutory and regulatory requirements.

We also are proposing to add § 314.93(e)(1)(vi) to codify our longstanding policy that FDA will not approve a suitability petition if a drug product is approved in an NDA for the change described in the petition. The suitability petition process is intended for a proposed “drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug” (§ 314.93(b)). If a pharmaceutically equivalent drug product has been approved in an NDA, the ANDA applicant should refer to the approved pharmaceutical equivalent designated by the Agency as the RLD as its basis for ANDA submission. Throughout

the pendency of review of the ANDA, applicants should confirm that an NDA has not been approved for the drug product described in the suitability petition.

Although FDA currently has the authority to withdraw approval of a suitability petition after a drug product is approved in an NDA for the change described in the petition, we note that it has been the Agency's practice not to rescind approval of the petition under these circumstances due to the administrative burden. We previously have explained: "we need not withdraw approval of the suitability petition to implement our long-standing practice that the intervening approval of an NDA for the product described by the suitability petition precludes an ANDA applicant from referring to the suitability petition and listed drug described therein as its basis for ANDA submission. Any pending ANDA that referred to the suitability petition and the listed drug described therein would not be eligible for approval, and any newly submitted ANDA that sought to reference the suitability petition instead of the RLD identified in the Orange Book would not be received by the Agency" (Venlafaxine ER Citizen Petition Response at 25). To ensure that our regulations consistently reflect this policy, we are proposing to add § 314.127(a)(14) to state that FDA will refuse to approve a petitioned ANDA if an NDA subsequently has been approved for the change described in the suitability petition.

II.J. Filing an NDA and Receiving an ANDA (Proposed § 314.101)

II.J.1. Notification of Filing of a 505(b)(2) Application or Receipt of an ANDA

We are proposing to amend § 314.101, with respect to 505(b)(2) applications and ANDAs that contain a paragraph IV certification, to facilitate implementation of the MMA's timing requirements for sending notice of a paragraph IV certification and for efficient enforcement of the FD&C Act.

Section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act require a 505(b)(2) or ANDA applicant, respectively, to send notice of a paragraph IV certification within 20 days after the date of the postmark on the notice with which FDA informs the applicant that the 505(b)(2) application has been filed or the ANDA has been received (see section II.D.1). Our proposed revisions to § 314.101(a)(2) and (b)(2) clarify that FDA will notify the applicant that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received, respectively, by means of an acknowledgment letter or a paragraph IV acknowledgment letter (see also section II.A.2.c and II.A.2.u).

We are proposing to revise § 314.101(b)(1) and (b)(2) regarding ANDAs to incorporate the statutory definition of a “substantially complete application,” which was added by the MMA for purposes of section 505(j)(5) of the FD&C Act (see section 505(j)(5)(B)(iv)(II)(cc) of the FD&C Act and section II.A.2.cc of this document). Proposed § 314.101(b)(1) states that receipt of an ANDA means that FDA has made a threshold determination that the ANDA is substantially complete. We also are proposing to revise proposed § 314.101(b)(2) to clarify that if an ANDA is determined to have been substantially complete as of the date on which it was submitted, the date of submission is considered to be the date of receipt. As noted in section II.A.2.cc, our proposed replacement of the current standard “sufficiently complete to permit a substantive review” with the phrase “substantially complete application” is not intended to alter the meaning. Rather, we are seeking to consistently use defined terms throughout our regulations.

We are proposing to amend § 314.101(b)(3) to remove the method of notification by which FDA will advise an ANDA applicant that FDA has refused to receive the ANDA under § 314.101(d) or (e). The regulations currently state that FDA will ordinarily notify an ANDA

applicant by telephone; however, this does not accurately describe FDA's current practice to inform the ANDA applicant in writing by issuing a "refuse to receive" letter.

In proposed § 314.101(b)(4), we establish an administrative consequence for an ANDA applicant that fails to timely provide notice of a paragraph IV certification as required by section 505(j)(2)(B)(ii) of the FD&C Act and § 314.95(b) and (d). If FDA determines that an ANDA applicant did not send notice of a paragraph IV certification within the timeframe described in § 314.95(b) or (d), as applicable, FDA will deem the date that the ANDA was submitted to be delayed by the number of days by which the timeframe for sending notice of a paragraph IV certification was exceeded. As discussed in section II.D.5, an ANDA applicant that fails to provide timely notice of a paragraph IV certification may, based upon the revised date on which the ANDA was determined to have been received, lose its first applicant status and thus its eligibility for 180-day exclusivity. In addition, such an ANDA may be repositioned in the review queue consistent with the revised date of ANDA submission.

II.J.2. Other Proposed Revisions

We are proposing several clarifying revisions to § 314.101. First, we are proposing to delete the reference to section 507 of the FD&C Act in § 314.101(d)(3). As discussed in section II.A.2.b, FDAMA repealed section 507 of the FD&C Act under which marketing applications, including abbreviated applications, for antibiotics had been approved (see section 125 of FDAMA). Section 125(d) of FDAMA provided that abbreviated applications for antibiotics previously approved under section 507 of the FD&C Act would be deemed approved under section 505(j) of the FD&C Act.

Second, we are proposing to replace the term "application" in § 314.101(d)(6) and (d)(7) with "NDA and ANDA" to clarify that these provisions apply to ANDAs as well as NDAs. As

discussed in section II.A.2.b and II.A.2.i, we have proposed to incorporate the commonly used acronyms NDA and ANDA in place of the terms application and abbreviated application, as appropriate, throughout the sections of part 314 and part 320 in this rulemaking. Proposed § 314.101(d)(6) states that FDA may refuse to file an NDA or may not consider an ANDA to be received if the NDA or ANDA does not contain a statement for each nonclinical laboratory study regarding compliance with the requirements of part 58 of this chapter. This criterion is applicable to ANDAs as well as NDAs. Nonclinical studies submitted in an ANDA may include, but are not limited to, dissolution studies and “dose-dumping” studies. Proposed § 314.101(d)(7) provides that FDA may refuse to file an NDA or may not consider an ANDA to be received if the NDA or ANDA does not contain a statement for each clinical study regarding whether it was conducted in compliance with the regulations in part 50 and part 56 of this chapter. Clinical studies submitted in an ANDA which may be subject to the regulations in part 50 and part 56 of this chapter include, for example, comparative clinical trials conducted for the purpose of demonstrating bioequivalence (see § 320.24(b)(4); see also § 314.94(a)(7)(iii)).

Third, we are proposing to replace the current text of § 314.101(e)(2) with a statement that FDA will refuse to file a 505(b)(2) application or will consider an ANDA not to have been received if submission of a 505(b)(2) application or an ANDA for the active moiety is not permitted under § 314.108(b)(2). This is not a substantive revision, as § 314.108(b)(2) describes the conditions set forth in current § 314.101(e)(2)(i) and (e)(2)(ii).

We also propose to add headings to certain paragraphs for administrative convenience.

II.K. Approval of an NDA and ANDA (Proposed § 314.105)

We are proposing to revise § 314.105(a) and (d) regarding approval of an NDA (including a 505(b)(2) application) and an ANDA to remove the references to a “delayed

effective date” and clarify that an application is approved on the date of issuance of an approval letter. These proposed revisions reflect current FDA practice and policy with respect to approval letters. The Agency does not issue approval letters with delayed effective dates. Rather, the Agency will issue a tentative approval letter when an NDA or ANDA that is otherwise eligible for approval cannot be approved due to unexpired patents, certain circumstances related to patent litigation (see § 314.107(b)(3) and (e)(1)(vi)), or various types of exclusivity (see proposed § 314.107(b)(1)(iii), (c) and (d)). “Tentative approval” is defined in proposed § 314.3. We also have made conforming revisions throughout this proposed rulemaking to replace references to the “effective date” of an application with language reflecting our current practice.

A drug product granted tentative approval is not an approved drug. Prior to obtaining approval of a 505(b)(2) application or ANDA, the applicant may be requested to submit updated labeling; chemistry, manufacturing, and controls (CMC) data; a safety update; and any other information necessary to ensure that the 505(b)(2) application or ANDA meets the statutory and regulatory requirements for approval. For a 505(b)(2) application or ANDA to be approved, the applicant must receive an approval letter from FDA (see proposed § 314.107(b)(4)).

We note that an applicant with a tentatively approved 505(b)(2) application or ANDA has a continuing obligation to amend its patent certification or statement if, at any time before approval of the 505(b)(2) application or ANDA, the submitted certification is no longer accurate (see proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii)). In the context of a tentatively approved application, this obligation may apply, for example, if the NDA holder for the listed drug relied upon or RLD timely submits new patent information for a patent that claims the drug substance, drug product, or a method of use after the 505(b)(2) application or ANDA has been tentatively approved. In this scenario, the 505(b)(2) or ANDA applicant would be required to submit an

amendment to its tentatively approved application with an appropriate patent certification or statement regarding the newly listed patent.

The applicant with a tentatively approved application also may need to update the draft product labeling to incorporate relevant revisions to the labeling of the listed drug relied upon or RLD made after the tentative approval of the 505(b)(2) application or ANDA, respectively. This caveat is particularly relevant for an ANDA, which is required by statute to have, among other things, the same labeling and conditions of use as the RLD (see section 505(j)(2)(A)(i) and (j)(2)(A)(v) of the FD&C Act; compare section 505(j)(10) of the FD&C Act), unless the ANDA applicant is not seeking approval for an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the FD&C Act (see § 314.94(a)(8)(iv); see also section 505(j)(2)(A)(viii) of the FD&C Act). In addition, a tentatively approved ANDA for a drug product intended for parenteral, ophthalmic, otic, or topical use that is required to contain the same inactive ingredients in the same concentration as the RLD, subject to exceptions specified in § 314.94(a)(9)(iii) through (a)(9)(v), may be required to modify its drug product and amend its ANDA to address certain changes in the formulation of the RLD subsequent to tentative approval unless FDA has made a determination that the RLD was not withdrawn from sale for reasons of safety or effectiveness (see §§ 314.122 and 314.161; see also discussion in section II.L).

In addition, we are proposing to revise § 314.105(a) and (d) to expressly state that FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application or ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of

the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention.

Finally, it should be noted that a tentatively approved application is subject to any applicable period of marketing exclusivity granted to the listed drug relied upon (for a 505(b)(2) application) or RLD (for an ANDA) after tentative approval. For example, approval of a tentatively approved application may be delayed by the intervening grant, pursuant to section 505A of the FD&C Act, of a period of pediatric exclusivity to the NDA holder for the listed drug relied upon or RLD after tentative approval of the 505(b)(2) application or ANDA, respectively (see, e.g., Barr Labs., Inc. v. Thompson, 238 F. Supp. 2d 236 (D.D.C. 2002) (upholding FDA's determination that a 6-month period of pediatric exclusivity that had attached to a listed patent for which a paragraph III certification had been submitted applied to a tentatively approved application)).

II.L. Refusal to Approve an NDA or ANDA (Proposed §§ 314.125 and 314.127 and Related Provisions in Proposed §§ 314.90 and 314.99)

We are proposing to revise §§ 314.90 and 314.99 to clarify the effect of FDA's grant of an applicant's request for waiver of a requirement under §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively. If FDA grants such a request, the applicant's failure to comply with the requirement that is the subject of the waiver request will not constitute a basis for refusal to approve the NDA under § 314.125 or the ANDA under § 314.127, as applicable. We also are proposing corresponding revisions to §§ 314.125(b) and 314.127(a), which address permissive refusal to approve an NDA and mandatory refusal to approve an ANDA, respectively. Proposed § 314.125(b) states that FDA may refuse to approve an NDA for any of the following reasons listed, unless the requirement has been waived pursuant to § 314.90.

Proposed § 314.127(a) states that FDA will refuse to approve an ANDA for a new drug under section 505(j) of the FD&C Act for any of the following reasons listed, unless the requirement has been waived pursuant to § 314.99.

Sections 314.90 and 314.99 currently provide that an NDA or ANDA applicant may ask FDA to waive any requirement that applies to the applicant under §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively. FDA has interpreted its waiver of a submission requirement under these provisions to carry with it the implicit waiver of any corresponding approval requirement under §§ 314.125 or 314.127. Otherwise, the waiver of a submission requirement for an NDA or ANDA would be meaningless if there was a parallel requirement under §§ 314.125 or 314.127, respectively, for approval of the application.

The proposed revisions to §§ 314.90 and 314.99, and corresponding proposed revisions to proposed §§ 314.125 and 314.127, codify FDA's approach to this issue. For example, FDA has relied on § 314.99(b) to grant a waiver of the requirement that the formulation of a drug product intended for parenteral use contain the same inactive ingredients in the same concentration as the RLD, with limited exceptions for preservatives, buffers, and antioxidants, where the formulation proposed by the ANDA applicant had previously been approved by FDA as safe and effective. We note that FDA may not waive a statutory requirement (see 1989 Proposed Rule, 54 FR 28872 at 28889).

II.M. Date of Approval of a 505(b)(2) Application or ANDA (Proposed § 314.107)

Section 314.107 establishes the earliest date on which a 505(b)(2) application or ANDA may be approved in light of the statutory provisions that can delay the approval of an application that is otherwise eligible for approval. Approval of a 505(b)(2) application or ANDA can be delayed by the marketing exclusivity granted to another drug product under section 505(c)(3)(E)

and (j)(5)(F) of the FD&C Act (and, with respect to ANDAs, section 505(j)(5)(B)(iv) of the FD&C Act for 180-day exclusivity) or pediatric exclusivity under section 505A of the FD&C Act that may attach to a patent listed for a drug product. Approval of a 505(b)(2) application or ANDA also can be delayed by a 30-month stay of approval should the NDA holder or patent owner initiate patent infringement litigation within the statutory timeframe in response to notice of a paragraph IV certification (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act). The MMA amended the FD&C Act to alter the circumstances under which a 30-month stay of approval can arise. The MMA also amended the FD&C Act to specify the types of court actions that will terminate a 30-month stay of approval. In addition, approval of a 505(b)(2) application or ANDA can be delayed by a court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that the application may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in § 314.107(b)(3) (see proposed § 314.107(b)(4) and (e)(1)(vi)).

Table 12 summarizes the proposed changes related to the effect of patent(s) on the listed drug with respect to the date of approval of a 505(b)(2) application or ANDA.

Table 12.--Highlights of Proposed Changes Regarding the Effect of Patent(s) on the Listed Drug¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Effect of patent on the listed drug (§ 314.107(b))</u></p> <ul style="list-style-type: none"> • Introduction to criteria for determining date on which approval of a 505(b)(2) application or ANDA will become effective. <p><u>Multiple certifications (§ 314.107(b)(4))</u></p> <ul style="list-style-type: none"> • If the applicant has submitted certifications for more than one patent, the date of approval will be calculated for each certification, and the approval will become effective on the last applicable date. 	<p><u>Effect of patent(s) on the listed drug (§ 314.107(b))</u></p> <ul style="list-style-type: none"> • Introduction to criteria that must be used to determine, for each relevant patent, the date that patent will no longer prevent approval. • The first possible date of approval will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.
<p><u>Date of approval letter (§ 314.107(b)(1))</u></p> <ul style="list-style-type: none"> • Except as provided in § 314.107(b)(3), (b)(4), and (c), approval will become effective on the date FDA issues an approval letter if the applicant certifies that: <ul style="list-style-type: none"> (i) there are no relevant patents; or (ii) the patent information has not been submitted to FDA; or (iii) the relevant patent has expired; or (iv) the relevant patent is invalid, unenforceable, or will not be infringed. 	<p><u>Timing of approval based on patent certification or statement (§ 314.107(b)(1))</u></p> <ul style="list-style-type: none"> • If none of the reasons in § 314.125 or § 314.127 for refusing to approve the application apply, and none of the reasons in § 314.107(d) for delaying approval apply, the 505(b)(2) application or ANDA may be approved-- <ul style="list-style-type: none"> (i) <u>Immediately</u>, if the applicant certifies that: <ul style="list-style-type: none"> (A) the patent information has not been submitted to FDA; or (B) the relevant patent has expired; or (C) the relevant patent is invalid, unenforceable, or will not be infringed, except as provided in § 314.107(b)(3) and (c), and the 45-day period provided for in section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act has expired; or (D) there are no relevant patents. (ii) <u>Immediately</u>, if the applicant submits an appropriate statement explaining that a method-of-use patent does not claim an indication or other condition of use for which it is seeking approval.
<p><u>Patent expiration (§ 314.107(b)(2))</u></p> <ul style="list-style-type: none"> • If the applicant certifies that the relevant patent will expire on a specified date (paragraph III certification), approval will become effective <u>on</u> the specified date. 	<p><u>Timing of approval based on patent certification or statement (§ 314.107(b)(1)(iii))</u></p> <ul style="list-style-type: none"> • If the applicant certifies that the relevant patent will expire on a specified date (paragraph III certification), a 505(b)(2) application or ANDA otherwise eligible for approval may be approved <u>on</u> the specified date.

Table 12.--Highlights of Proposed Changes Regarding the Effect of Patent(s) on the Listed Drug¹

Current Regulations	Proposed Revisions to Regulations
<p>[No corresponding regulation]</p>	<p><u>Patent information filed after submission of 505(b)(2) application or ANDA (§ 314.107(b)(2))</u></p> <ul style="list-style-type: none"> • If an NDA holder submits patent information for a listed drug after the date on which a 505(b)(2) application or ANDA relying on such drug was submitted to FDA, the 505(b)(2) or ANDA applicant must submit an amended patent certification or statement in accordance with §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii). • If the applicant submits a paragraph IV certification to the newly-listed patent information and complies with the notice requirements of § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification. • The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act does not apply.
<p><u>Disposition of patent litigation (§ 314.107(b)(3)(i))</u></p> <ul style="list-style-type: none"> • (A) Except as provided in § 314.107(b)(3)(ii) through (b)(3)(iv), if <ul style="list-style-type: none"> -- applicant submits a paragraph IV certification; and -- patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt by the patent owner of the notice of paragraph IV certification, Approval may be made effective 30 months after the date of the receipt of the notice of paragraph IV certification by the patent owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period; or • (B) If the patented drug product qualifies for 5-year exclusivity, and <ul style="list-style-type: none"> -- patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt by the patent owner of the notice of paragraph IV certification, Approval may be made effective at the expiration of 7½ years from the date of NDA approval for the patented drug product. 	<p><u>Disposition of patent litigation (§ 314.107(b)(3)(i))</u></p> <ul style="list-style-type: none"> • (A) Except as provided in § 314.107(b)(3)(ii) through (b)(3)(viii), if, with respect to patents for which required information was submitted before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement), <ul style="list-style-type: none"> --applicant submits a paragraph IV certification; and --patent owner or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of paragraph IV certification, 505(b)(2) application, or ANDA may be approved 30 months after the later of the date of the receipt of the notice of certification by any owner of the listed patent or by the NDA holder who is an exclusive patent licensee (or their representatives) unless the court has extended or reduced the period; or • (B) If the patented drug product qualifies for 5-year exclusivity, and <ul style="list-style-type: none"> --patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved at the expiration of 7½ years from the date of NDA approval for the patented drug product.

Table 12.--Highlights of Proposed Changes Regarding the Effect of Patent(s) on the Listed Drug¹

Current Regulations	Proposed Revisions to Regulations
<p data-bbox="191 258 516 289"><u>Disposition of patent litigation</u> (§ 314.107(b)(3)(ii)-(b)(3)(iv))</p> <p data-bbox="191 317 727 373">If before the expiration of the 30-month period, or 7½ years where applicable:</p> <ul data-bbox="191 411 727 1115" style="list-style-type: none"> <li data-bbox="191 411 727 562">• (ii) the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on: -- the date the court enters judgment; <li data-bbox="191 600 727 751">• (iii) the court issues a final order or judgment that the patent has been infringed, approval may be made effective on: -- the date the court determines that the patent will expire or otherwise orders <li data-bbox="191 789 727 1115">• (iv) the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid, unenforceable, or not infringed, approval may be made effective on: -- the date the court enters a final order or judgment that the patent is invalid, unenforceable, or not infringed. 	<p data-bbox="755 258 1307 315"><u>Disposition of patent litigation (§ 314.107(b)(3)(ii)-(b)(3)(viii))</u></p> <p data-bbox="755 317 1388 373">If before the expiration of the 30-month period, or 7½ years where applicable:</p> <ul data-bbox="755 411 1388 1822" style="list-style-type: none"> <li data-bbox="755 411 1388 751">• (ii) the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on: --(A) the date on which the court enters judgment reflecting the decision; or --(B) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed. <li data-bbox="755 789 1388 1056">• (iii) the district court decides that the patent has been infringed and the judgment is appealed, the 505(b)(2) application or ANDA may be approved on: --(A) the date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid or not infringed; or --(B) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent is invalid or not infringed. <li data-bbox="755 1094 1388 1245">• (iv) the district court decides that the patent has been infringed and the judgment is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A). <li data-bbox="755 1283 1388 1644">• (v) the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement: -- if the court later decides the patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved per § 314.107(b)(3)(ii). --if the court decides that the patent has been infringed, the 505(b)(2) application or ANDA may be approved per § 314.107(b)(3)(iii) or (b)(3)(iv), as applicable. <li data-bbox="755 1682 1388 1822">• (vi) the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

Table 12.--Highlights of Proposed Changes Regarding the Effect of Patent(s) on the Listed Drug¹

Current Regulations	Proposed Revisions to Regulations
	<ul style="list-style-type: none"> • (vii) the court enters an order requiring the 30-month or 7½-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order. • (viii) the court enters an order of dismissal, with or without prejudice, without a finding of infringement, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

II.M.1. General (Proposed § 314.107(a))

We are not proposing any substantive revisions to § 314.107(a). As noted in section II.A.2.dd and II.I, we are proposing to amend references to the “effective date of approval” and the date the approval of a 505(b)(2) application or ANDA “becomes effective” to simply refer to the date the 505(b)(2) application or ANDA “is approved.” The current text incorrectly suggests that FDA might issue an approval letter that would become effective at some date in the future. The proposed revision clarifies that a 505(b)(2) application or ANDA is not approved until the date the Agency issues its approval letter.

II.M.2. Effect of Patent(s) on the Listed Drug (Proposed § 314.107(b))

We are proposing to revise the introduction to proposed § 314.107(b) to clarify that an analysis is required for each relevant patent to determine the effect of one or more patents listed for the listed drug(s) relied upon or the RLD on the date of approval of a 505(b)(2) application or ANDA, respectively. For each relevant patent, the patent certification or statement submitted by the 505(b)(2) or ANDA applicant is reviewed to determine the first possible date of approval based upon each patent. The 505(b)(2) application or ANDA may be approved on the last applicable date for all relevant patents. This approach to the evaluation of multiple patent

certifications is described in current § 314.107(b)(4), which is proposed for deletion because the substance of that paragraph is in proposed § 314.107(b).

II.M.2.a. Timing of approval based on patent certification or statement (proposed § 314.107(b)(1)). We are proposing to amend § 314.107(b)(1) to describe, in a more comprehensive manner, the timing of approval of a 505(b)(2) application or ANDA based on the patent certification(s) or statement(s) submitted by the 505(b)(2) or ANDA applicant. As explained in proposed § 314.107(b)(1), the timing of approval based on an analysis of an applicant's patent certification(s) or statement(s) is directed to a 505(b)(2) application or ANDA that is otherwise eligible for approval. A 505(b)(2) application or ANDA is otherwise eligible for approval if none of the reasons in § 314.125 or § 314.127 for refusing to approve the 505(b)(2) application or ANDA applies, and if no delay is required by the exclusivity provisions of § 314.108, § 316.31, or section 505A of the FD&C Act (see section II.I).

In proposed § 314.107(b)(1)(i) and (b)(1)(ii), we describe the types of patent certifications or statements that would result in an immediate first possible date of approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval. Proposed § 314.107(b)(1)(i) reflects a reorganization of the current regulation and not a substantive revision. Current § 314.107(b)(i) through (b)(iv) are redesignated as proposed § 314.107(b)(1)(i)(A) through (b)(1)(i)(D)). We have proposed to move the phrase “except as provided in paragraphs (b)(3) and (c)” from the introduction to current § 314.107(b)(1) to § 314.107(b)(1)(i)(C) to more closely associate this very important and common exception to an immediate date of approval with the paragraph that describes a paragraph IV certification. In addition, we are proposing to clarify that a 505(b)(2) application or ANDA containing a

paragraph IV certification may be approved immediately only if the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act has expired.

We are proposing to revise § 314.107(b)(1)(ii) (the current text of which is proposed for incorporation into § 314.107(b)(1)(i)) to clarify that an appropriate statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) also could result in an “immediate” first possible date of approval. This proposed revision addresses an omission in the current regulations. A 505(b)(2) or ANDA applicant may submit a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii), respectively, explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval (see section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act). If the patent only claims the method of use for which the 505(b)(2) or ANDA applicant submitted a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii), respectively, then a 505(b)(2) application or ANDA otherwise eligible for approval may be approved immediately.

As described in section II.B.1.a, a listed patent may claim the drug substance and/or drug product in addition to one or more methods of use, and a 505(b)(2) or ANDA applicant could submit a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) with respect to one or more methods of use and a paragraph IV certification with respect to the remaining drug substance and/or drug product claims and/or any additional methods of use. In this scenario, the applicant’s paragraph IV certification and statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) to the patent would be analyzed in accordance with proposed § 314.107(b)(1)(i)(C) and (b)(1)(ii) to determine whether the first possible date of approval for the 505(b)(2) application or ANDA based on this patent is “immediately” or whether the exceptions described in § 314.107(b)(3) and (c) apply with respect to the paragraph IV

certification. Approval of a 505(b)(2) application or ANDA that contains a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) with respect to one or more methods of use and a paragraph IV certification with respect to the remaining patent claims may be subject to a 30-month stay (or 7½ years where applicable) if patent infringement litigation is initiated within the statutory timeframe with respect to the patent claims that were the subject of the paragraph IV certification (see § 314.107(b)(3)). It should be noted that if the paragraph IV certification that gave rise to the 30-month stay (or 7½ years where applicable) is subsequently amended to a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) with respect to one or more methods of use, the 30-month stay (or 7½ years where applicable) will not be terminated in the absence of a qualifying event under § 314.107(b)(3).

We are proposing to move § 314.107(b)(2) regarding paragraph III certifications, which delay approval until the date on which the patent will expire, to proposed § 314.107(b)(1)(iii) for organizational convenience. An analysis of the effect of patents on the timing of approval of a 505(b)(2) application or ANDA is made when the 505(b)(2) application or ANDA is otherwise eligible for approval.

II.M.2.b. Patent information filed after submission of 505(b)(2) application or ANDA (proposed § 314.107(b)(2)). We are proposing to revise § 314.107(b)(2) (redesignated as proposed § 314.107(b)(1)(iii)) to clarify the effect of patent information filed after submission of a 505(b)(2) application or ANDA on the date of approval of a 505(b)(2) application or ANDA. If an NDA holder submits patent information for a listed drug after the date on which a 505(b)(2) application or ANDA relying upon such drug was submitted to FDA, the 505(b)(2) or ANDA applicant must comply with the requirements of §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii) regarding amendment of its patent certification or statement (see section II.E.4).

Thus, if the patent information was timely filed by the NDA holder under § 314.53(d)(3), the 505(b)(2) or ANDA applicant would be required to amend its patent certification or statement for the listed drug relied upon or RLD, respectively, to address the newly listed patent. (A 505(b)(2) or ANDA applicant whose pending application did not contain an appropriate patent certification at the time of submission would be required to submit a patent certification or statement to the newly listed patent even if such patent information was filed by the NDA holder more than 30 days after patent issuance (i.e., untimely filed).)

If the 505(b)(2) or ANDA applicant submits an amendment containing a paragraph IV certification to the newly listed patent, proposed § 314.107(b)(2) clarifies that the 505(b)(2) application or ANDA may be approved immediately upon the submission of an amendment containing documentation that the NDA holder and each patent owner have received notice of paragraph IV certification under § 314.52(e) or § 314.95(e). There is no need to delay approval until the expiration of the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act. Even if the NDA holder or patent owner initiated patent infringement litigation within the 45-day period after receipt of notice of paragraph IV certification, a 30-month stay of approval would not be available in connection with a paragraph IV certification to a patent submitted after a 505(b)(2) application or ANDA had been submitted to FDA (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

Although a 30-month stay of approval is not available in these circumstances, a 505(b)(2) or ANDA applicant still must comply with the requirements for provision of notice of paragraph IV certification described in section 505(b)(3) and (j)(2)(B) of the FD&C Act and §§ 314.52 and 314.95. An NDA holder or patent owner may assert a claim of patent infringement against the 505(b)(2) or ANDA applicant in response to the notice of paragraph IV certification and may

seek injunctive relief during the pendency of the litigation despite the absence of a 30-month stay. Notice of paragraph IV certification in accordance with applicable regulations also is necessary for an ANDA applicant to be eligible for 180-day exclusivity based upon a paragraph IV certification to a newly listed patent (see section II.D.1).

II.M.2.c. Disposition of patent litigation (proposed § 314.107(b)(3)).

II.M.2.c.i. Approval upon expiration of 30-month stay or 7½ years from date of reference product approval (proposed § 314.107(b)(3)(i)). We are proposing to revise § 314.107(b)(3)(i)(A) to reflect one of the central elements of the MMA's amendments to the FD&C Act: The limitation on multiple 30-month stays of approval of a 505(b)(2) application or an ANDA containing a paragraph IV certification to certain patents submitted to FDA on or after August 18, 2003. Proposed § 314.107(b)(3)(i)(A) states that a 30-month stay of approval is available only when the patent owner or exclusive patent licensee initiates a patent infringement action within the statutory timeframe in response to a paragraph IV certification to a patent submitted to FDA before the date on which the original 505(b)(2) application or ANDA was submitted. As discussed in section II.E, the MMA expressly provides that, for purposes of determining the availability of a 30-month stay, the date of submission of a 505(b)(2) application or ANDA does not include the date of submission of an amendment or supplement to the 505(b)(2) application or ANDA (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act). In other words, there will be no possibility of a 30-month stay with respect to an action for infringement of a patent listed after the reference product is approved if the patent was submitted to FDA on or after the date the 505(b)(2) application or ANDA was first submitted. Due to this limitation, most 505(b)(2) applications and ANDAs will be subject to no more than one 30-month stay of approval.

Multiple 30-month stays, however, still may be possible in certain cases. For example, an original 505(b)(2) application or ANDA may contain a paragraph IV certification to a patent that results in a 30-month stay of approval. If the same application also contains a paragraph III certification to a different patent that was submitted to FDA on or after August 18, 2003, and before the 505(b)(2) application or ANDA was submitted, and the applicant subsequently amends the paragraph III certification to a paragraph IV certification, a second 30-month stay would be possible. Two 30-month stays are possible in this example because the challenged patents that gave rise to sequential actions for patent infringement were both submitted to FDA before submission of the original 505(b)(2) application or ANDA. It should be noted that the relevant benchmark for determining whether a patent was submitted by the NDA holder prior to submission of an original 505(b)(2) application or prior to submission of an ANDA later determined to be substantially complete is the date of submission of the patent to FDA and not the date on which the patent information is published in the Orange Book (see § 314.53(d)(5)). We note, however, that if the original submission of an ANDA is not determined to be substantially complete (i.e., FDA refuses to receive the ANDA under § 314.101), then the relevant benchmark is the date of the ANDA amendment that results in a subsequent determination that the ANDA is substantially complete.

We also are proposing to revise § 314.107(b)(3)(i) to clarify that a 30-month stay of approval begins on the later of the date of receipt of the notice of paragraph IV certification by any owner of the listed patent or by the NDA holder who is an exclusive patent licensee (or their representatives). This proposed revision codifies our current practice and provides an administratively efficient means of ensuring that each patent owner or NDA holder that is entitled to receive notice of paragraph IV certification receives the full statutory 30-month stay

of approval should one of these parties initiate patent infringement litigation within 45 days of its receipt of notice. Even if a patent infringement action was initiated within 45 days of receipt of notice of paragraph IV certification by the first of two intended recipients, the 30-month stay of approval would begin on the later of the dates of receipt of notice of paragraph IV certification by any owner of the listed patent or by the NDA holder.

Finally, we are proposing to revise § 314.107(b)(3) to supplement the list that describes different scenarios related to the timing of approval of a 505(b)(2) application or ANDA containing a paragraph IV certification that was the subject of patent litigation. Many of our proposed additions to the § 314.107(b) list reflect corresponding MMA amendments to section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act (see sections II.M.3.e to II.M.3.h). It should be noted that we are not proposing revisions to § 314.107(b)(3) to describe the date on which a 505(b)(2) application or ANDA may be approved when a 30-month stay relates to a patent to which pediatric exclusivity has attached (see section 505A of the FD&C Act). However, a period of pediatric exclusivity under section 505A of the FD&C Act may affect the approval date of a 505(b)(2) application or ANDA in the circumstances described in § 314.107(b)(3).

II.M.2.c.ii. Federal district court decision of invalidity, unenforceability, or non infringement (proposed § 314.107(b)(3)(ii)). The MMA amended section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act for 505(b)(2) applications and ANDAs, respectively, to clarify the type of court decision in patent litigation that will terminate a 30-month stay (or 7½ years where applicable) and lead to approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval. Prior to the MMA, FDA interpreted the reference to a court decision in section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act to mean “the court that enters final judgment from which no appeal can be or has been taken” (see guidance for industry entitled

“Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act” (March 2000), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072868.pdf> (superseded Guidance on Court Decisions). The MMA amended the FD&C Act to codify the types of Federal district court decisions and, as discussed in section II.M.2.c.iii to II.M.2.c.iv, the types of Federal appellate court decisions that will terminate a 30-month stay (or 7½ years where applicable). Accordingly, FDA is not required to delay approval of an otherwise approvable ANDA until there has been a court decision from which no appeal can be or has been taken.

The MMA amended section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act to describe the Federal district court decisions in patent litigation that will terminate a 30-month stay (or 7½ years where applicable) and lead to approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval (see Sanofi-Aventis v. FDA, 643 F.Supp.2d 82, 86 (D.D.C.), inj. denied, 2009 U.S. Dist. LEXIS 74578 (D.D.C. 2009) (“The plain language of the entry of judgment provision of the Hatch-Waxman Act is clear that the FDA’s approval of a generic application ‘shall be made effective on the ... date on which the court enters judgment’ ” irrespective of whether the enforceability of that judgment is stayed) (emphasis in original)). We are proposing to revise § 314.107(b)(3)(ii) to reflect these statutory revisions that change the decisive event from court issuance of a final order that the patent is invalid, unenforceable, or not infringed to a district court’s entry of judgment pursuant to Federal Rule of Civil Procedure (Fed. R. Civ. P.) Rule 58 that the patent is invalid, unenforceable, or not infringed. As with current § 314.107(b)(3)(ii), we are proposing to implement section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act to include a court decision that the applicable patent is unenforceable. Thus, a

Federal district court's entry of judgment that a patent has been infringed by the 505(b)(2) or ANDA applicant but is unenforceable (for example, due to inequitable conduct in patent prosecution) would terminate a 30-month stay (or 7½ years where applicable). Consistent with section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act, proposed § 314.107(b)(3)(ii) also includes cases in which a Federal district court has made a substantive determination that there is no cause of action for patent infringement or invalidity.

We are proposing to further revise § 314.107(b)(3)(ii) to incorporate the text of section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act, as amended by the MMA, regarding the timing of approval of a 505(b)(2) application or ANDA in relation to the district court decision. Proposed § 314.107(b)(3)(ii) provides that in cases in which a district court decides that the patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved on the date on which the court enters judgment reflecting the decision (paragraph (A)); or the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed (paragraph (B)).

II.M.2.c.iii. Appeal of Federal district court judgment of infringement (proposed § 314.107(b)(3)(iii)). The MMA amended section 505(c)(3)(C)(ii) and (j)(5)(B)(iii)(II) of the FD&C Act for 505(b)(2) applications and ANDAs, respectively, to describe the earliest date on which a 30-month stay (or 7½ years where applicable) can be terminated after a Federal district court has decided that the patent has been infringed based on whether the judgment is appealed. We are proposing to revise § 314.107(b)(3)(iii) and, as discussed in section II.M.2.c.iv, § 314.107(b)(3)(iv) to reflect these statutory revisions.

Proposed § 314.107(b)(3)(iii) states that if the Federal district court decides that the patent has been infringed and the district court judgment is appealed, the 505(b)(2) application or

ANDA may be approved on the date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity) (paragraph (A)); or the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed (paragraph (B)). Proposed § 314.107(b)(3)(iii) restates the text of section 505(c)(3)(C)(ii) and (j)(5)(B)(iii)(II) of the FD&C Act except that we are proposing to further specify that the date of the court of appeals decision is the date on which the mandate is issued by the court of appeals (see Federal Rule of Appellate Procedure Rule 41). This proposal reflects the Agency's current practice in implementing section 505(c)(3)(C)(ii) and (j)(5)(B)(iii)(II) of the FD&C Act, which recognizes that a party may request rehearing by the appellate panel or rehearing en banc. In such circumstances, it would be premature to terminate the 30-month stay and possibly approve the 505(b)(2) application or ANDA while a decision regarding patent noninfringement, invalidity, or unenforceability was being reheard by the court of appeals. By interpreting the "date on which the court of appeals decides that the patent is invalid or not infringed" (see section 505(c)(3)(C)(ii) and (j)(5)(B)(iii)(II) of the FD&C Act) to mean the date on which the mandate issues, we are ensuring that the Agency's action reflects the judgment of the court of appeals. We seek comment on this interpretation.

II.M.2.c.iv. Affirmation or non-appeal of Federal district court judgment of infringement (proposed § 314.107(b)(3)(iv)). The MMA amended section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act to describe the timing of approval of a 505(b)(2) application or ANDA, respectively, that a Federal district court has decided infringes a patent that was the subject of a paragraph IV certification if the district court decision was not appealed

or was affirmed on appeal. In such a case, section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act provide that the 505(b)(2) application or ANDA will be approved on the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A). We are proposing to revise § 314.107(b)(3)(iv) to reflect these statutory revisions with certain clarifications.

Proposed § 314.107(b)(3)(iv) provides that if the district court decides that the patent at issue is infringed and this judgment is not appealed or is affirmed on appeal, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A). Although the date specified by the district court order would not be earlier than the date of expiration of the infringed patent (see 35 U.S.C. 271(e)(4)(A)), the date specified by the order may not take into account any other unexpired patents or unexpired exclusivity (or deficiencies in the application) that would delay approval of the 505(b)(2) application or ANDA beyond the date of expiration of the infringed patent. Therefore, proposed § 314.107(b)(3)(iv) states that the 505(b)(2) application or ANDA may be approved no earlier than the date specified in a district court's order under 35 U.S.C. 271(e)(4)(A), rather than using the statutory phrasing that the "approval shall be made effective on the date" specified by such order (see section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act and section II.I regarding removal of references to the effective date of approval).

II.M.2.c.v. Grant of preliminary injunction by Federal district court (proposed § 314.107(b)(3)(v)). The MMA amended section 505(c)(3)(C)(iii), (c)(3)(C)(iv), (j)(5)(B)(iii)(III), and (j)(5)(B)(iii)(IV) of the FD&C Act to clarify that the timing of approval of a 505(b)(2) application or ANDA, respectively, is subject to provisions of section 505(c)(3)(C)(i), (c)(3)(C)(ii), (j)(5)(B)(iii)(I), and (j)(5)(B)(iii)(II) even if preceded by a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or

sale of the drug until the court decides the issues of patent validity and infringement. We are proposing to revise current § 314.107(b)(3)(iv) (redesignated as proposed § 314.107(b)(3)(v)) to reflect these statutory revisions. Proposed § 314.107(b)(3)(v) cross-references the applicable paragraph of § 314.107(b)(3) that would address the timing of approval of the 505(b)(2) application or ANDA based on the court's decision with respect to patent validity and infringement. If a preliminary injunction is entered before the expiration of the 30-month stay, FDA interprets section 505(j)(5)(B)(iii) of the FD&C Act to require that the stay of approval is extended until the court decides the issues of patent infringement and validity. Once such a decision is made, the references to section 505(j)(5)(B)(iii)(I) and (j)(5)(B)(iii)(II) of the FD&C Act provide for the timing of approval (see section 505(j)(5)(B)(iii)(III) and (j)(5)(B)(iii)(IV) of the FD&C Act). We seek comment on this approach.

In addition, proposed § 314.107(b)(3)(v) makes clear that the court that grants a preliminary injunction pending a decision on the issues of patent validity and infringement refers to the Federal district court hearing the patent infringement action.

II.M.2.c.vi. Written consent to approval by patent owner or exclusive patent licensee (proposed § 314.107(b)(3)(vi)). We are proposing to add § 314.107(b)(3)(vi) to clarify that if the patent owner or exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA application may be approved, the 30-month stay (or 7½ years where applicable) will be terminated and the approval may be granted on or after the date of the consent. Thus, proposed § 314.107(b)(3)(vi) would permit termination of the 30-month stay (or 7½ years where applicable) without a court order. This scenario may arise, for example, if settlement of the patent litigation results in a license to the 505(b)(2) or ANDA applicant.

II.M.2.c.vii. Court order terminating 30-month or 7½-year period (proposed § 314.107(b)(3)(vii)). We are proposing to add § 314.107(b)(3)(vii) to clarify that if a court enters an order requiring the termination of the 30-month stay (or 7½ years where applicable), the 505(b)(2) application or ANDA, if otherwise ready for approval, may be approved in accordance with the court order.

II.M.2.c.viii. Court order of dismissal without a finding of infringement (proposed § 314.107(b)(3)(viii)). The MMA's amendments to section 505(c)(3)(C)(i), (c)(3)(C)(ii), (j)(5)(B)(iii)(I), and (j)(5)(B)(iii)(II) of the FD&C Act clarify the timing of approval of a 505(b)(2) application or ANDA, respectively, in relation to a settlement order or consent decree stating that the patent that is the subject of the paragraph IV certification is invalid or not infringed. However, the statute does not address whether a 30-month stay may be terminated and a 505(b)(2) application or ANDA approved if the court enters an order of dismissal without a finding of patent infringement--a scenario that FDA encounters frequently. We are proposing to add § 314.107(b)(3)(viii) to codify FDA's policy that court entry of an order of dismissal, with or without prejudice, of patent infringement litigation that was timely initiated in response to notice of a paragraph IV certification will terminate the 30-month period (or 7½ years where applicable) if such order does not state a finding of patent infringement. It is appropriate that a 30-month stay terminates under these circumstances because the statutory purpose of the stay is to allow time for claims of patent infringement to be litigated prior to approval of the potentially infringing drug product. If the patent owner or exclusive patent licensee dismisses the patent infringement action on terms that the court considers proper (see Fed. R. Civ. P. Rule 41(a)(2)), then there should be no further delay of approval of a 505(b)(2) application or ANDA otherwise eligible for approval.

II.M.2.d. Tentative approval (proposed § 314.107(b)(4)). We are proposing to redesignate current § 314.107(b)(3)(v) as proposed § 314.107(b)(4) for organizational convenience. Proposed § 314.107(b)(4) describes tentative approval of a 505(b)(2) application or ANDA as appropriate in accordance with § 314.107(b)(3). In addition, we are proposing to revise § 314.107(b)(4) to state that FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with a court order pursuant to 35 U.S.C. 271(e)(4)(A) that a 505(b)(2) application or ANDA may be approved no earlier than the date specified, irrespective of whether the injunction relates to a patent described in § 314.107(b)(3) (see proposed § 314.107(e)(1)(vi)). This proposed revision is intended to complement proposed § 314.107(g), which clarifies that if a court enters an order requiring that the date of approval be delayed for an already approved 505(b)(2) application or ANDA, FDA will convert the approval to a tentative approval, if appropriate. This scenario may occur, for example, if a patent infringement action is initiated after the 45-day period described in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act and results in a judgment of patent infringement. Proposed § 314.107(b)(4) would expressly describe FDA's practice of giving effect to the court order under 35 U.S.C. 271(e)(4)(A), irrespective of whether the order relates to a patent associated with a 30-month stay of approval (see, e.g., Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004)).

We also are proposing to amend references to “receiv[ing] final approval” and making an approval “effective” to refer instead to receipt of an approval letter (see sections II.A.2.dd and II.I).

II.M.3. Subsequent ANDA Submission (Proposed § 314.107(c))

Section 1102 of the MMA amended section 505(j)(5) of the FD&C Act to modify the conditions under which a 180-day period of exclusivity is granted and to establish conditions under which a first applicant would forfeit the 180-day exclusivity period. As noted in section I.D, we are currently implementing the 180-day exclusivity provisions of the MMA directly from the statute and will determine if additional rulemaking is necessary in the future. At this time, we are proposing to revise § 314.107(c) to remove provisions that have been superseded by the statute, as revised by the MMA, and to generally conform with the statute.

Table 13 summarizes the proposed changes related to submission of an ANDA containing a paragraph IV certification by a subsequent ANDA applicant.

Table 13.--Highlights of Proposed Changes Regarding Subsequent ANDA Submission¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Subsequent ANDA submission (§ 314.107(c)(1),(3))</u></p> <ul style="list-style-type: none"> • If an ANDA contains a paragraph IV certification and the ANDA is for a generic copy of the same listed drug for which one or more substantially complete ANDAs were previously submitted containing a paragraph IV certification to the same patent, approval of the subsequent ANDA will be made effective no sooner than 180 days from whichever of the following dates is earlier: <ul style="list-style-type: none"> --(i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or --(ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed. • For purposes of § 314.107(c)(1), if FDA concludes that the applicant submitting the first ANDA is not actively pursuing approval, FDA will make the approval of subsequent ANDAs immediately effective if they are otherwise eligible for an immediately effective approval. 	<p><u>Subsequent ANDA submission (§ 314.107(c)(1))</u></p> <ul style="list-style-type: none"> • If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as that of a subsequent applicant. • The ANDA of a subsequent applicant will not be approved during the period when any first applicant for the drug product is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant. • Any applicable 180-day exclusivity period can not extend beyond the expiration of the patent upon which the 180-day exclusivity period was based.
<p><u>Subsequent ANDA submission (§ 314.107(c)(2))</u></p> <ul style="list-style-type: none"> • For purposes of § 314.107(c)(1), the ‘applicant submitting the first application’ is the applicant that submits an ANDA that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. • A ‘substantially complete’ application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies. 	<p><u>Definitions (§ 314.3(b))</u></p> <ul style="list-style-type: none"> • <u>First applicant</u> is an applicant that, on the first day on which a substantially complete ANDA containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug. • <u>Substantially complete application</u> is an ANDA that on its face is sufficiently complete to permit a substantive review and contains all the information required under section 505(j)(2)(A) of the FD&C Act and § 314.94.

Table 13.--Highlights of Proposed Changes Regarding Subsequent ANDA Submission¹

Current Regulations	Proposed Revisions to Regulations
<u>Subsequent ANDA submission (§ 314.107(c)(4))</u> <ul style="list-style-type: none"> For purposes of § 314.107(c)(1)(i), the applicant submitting the first ANDA shall notify FDA of the date that it commences commercial marketing of its drug product. If an applicant does not promptly notify FDA of such date, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing. Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder. 	<u>Subsequent ANDA submission (§ 314.107(c)(2))</u> <ul style="list-style-type: none"> For purposes of § 314.107(c)(1), a first applicant must submit a supplement to its ANDA notifying FDA within 30 days of the date of first commercial marketing of its drug product. If an applicant does not notify FDA, as required above, of this date, the date of first commercial marketing will be deemed to be the date of the drug product's approval. <u>Definitions (§ 314.3(b))</u> <ul style="list-style-type: none"> <u>Commercial marketing</u> is the introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA, outside the control of the ANDA holder, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale to parties identified in the approved ANDA.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

We are proposing to revise § 314.107(c)(1) to incorporate the term “first applicant,” as defined by section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act and in proposed § 314.3(b) (see section II.A.2.q), and to distinguish a “first applicant” from a “subsequent applicant.” An ANDA has been submitted by a subsequent applicant if the ANDA has not been submitted by a first applicant and contains a paragraph IV certification to a relevant patent that has been listed for the drug product for which a first applicant has submitted an ANDA. A subsequent applicant's ANDA will not be approved during the period when any first applicant for the drug product is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant (see section 505(j)(5)(B)(iv)(I) of the FD&C Act). By including the period during which any first applicant is eligible for 180-day exclusivity, proposed § 314.107(c)(1) clarifies that a subsequent ANDA for the drug product may not be approved while a first applicant is eligible for 180-day exclusivity as long as a forfeiture event has not occurred with respect to that

first applicant (see section 505(j)(2)(D)(ii) of the FD&C Act). These proposed revisions replace the current text of § 314.107(c)(1), superseded by statute, which describe a patent-by-patent analysis to determine eligibility for 180-day exclusivity and events that would trigger the start of the 180-day period under the pre-MMA statutory scheme.

We are proposing to delete the definition of the “applicant submitting the first application” in current § 314.107(c)(2) because it has been superseded by the statutory definition added by the MMA. We are proposing to incorporate the MMA’s definition of the term “first applicant,” with minor editorial changes and additional clarifying text, into § 314.3(b) (see section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act and section II.A.2.q). We also are proposing to delete § 314.107(c)(3), which described the potential consequences of a first applicant’s failure to actively pursue approval of its ANDA because this regulation has been superseded by the statutory provisions that specify events that will result in forfeiture of the 180-day exclusivity period by a first applicant (see section 505(j)(5)(D) of the FD&C Act).

The MMA amended the FD&C Act to modify the types of events that can trigger the start of the 180-day exclusivity period for a first applicant (see section 505(j)(5)(B)(iv)(I) of the FD&C Act; see also section 1102(b)(3) of the MMA). Section 505(j)(5)(B)(iv)(I) of the FD&C Act provides that the period of 180-day exclusivity will begin on the “date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.” This commercial marketing trigger differs from the version of section 505(j)(5)(B)(iv)(I) in effect prior to enactment of the MMA, which provided that the 180-day exclusivity period will begin on the earlier of two events, one of which was the date the Secretary receives notice from the applicant of the first commercial marketing of the drug eligible for 180-day exclusivity. We are proposing to revise § 314.107(c)(4) to conform with

these changes to the FD&C Act and redesignate this provision as § 314.107(c)(2) (“redesignated § 314.107(c)(2)”).

In light of the change in the commercial marketing trigger from the date on which FDA receives notice from the applicant of the first commercial marketing to the date of the first commercial marketing of the drug, we are proposing to revise redesignated § 314.107(c)(2) to require a first applicant to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product (see current § 314.107(c)(4)). This proposal to require notification within 30 days of the date of first commercial marketing is intended to facilitate the efficient enforcement of the FD&C Act and provide adequate notice to subsequent applicants that have received tentative approval and are awaiting expiration of the period of 180-day exclusivity. If the first applicant does not notify FDA within this timeframe, we are proposing to deem the date of first commercial marketing to be the date of the drug product’s approval. This may have the effect of shortening the 180-day period of exclusivity in a manner similar to current § 314.107(c)(4).

We also are proposing to revise redesignated § 314.107(c)(2) to remove the description of “commercial marketing.” As explained in section II.A.2.1, we are proposing to define “commercial marketing” in § 314.3(b) with certain modifications, as compared to current § 314.107(c)(4), to the scope of the exclusion for transfer of the drug product for reasons other than sale.

II.M.4. Delay of Approval Due to Exclusivity (Proposed § 314.107(d))

We are proposing to revise § 314.107(d) to clarify that approval of a 505(b)(2) application or ANDA may be delayed by orphan drug exclusivity and pediatric exclusivity in addition to the exclusivities described in § 314.108. Proposed § 314.107(d) explains that when

approval of a 505(b)(2) application or ANDA is delayed under § 314.107 and § 314.108, 21 CFR 316.31 (orphan drug exclusivity), or section 505A of the FD&C Act (pediatric exclusivity), the 505(b)(2) application or ANDA will be approved on the latest of the dates specified under these provisions. We also have made conforming revisions to proposed § 314.107(d) that are described elsewhere in section II.M.

II.M.5. Notification of Court Actions or Documented Agreement (Proposed § 314.107(e))

We are proposing to revise § 314.107(e) to expand the scope of documentation that an applicant must submit to FDA regarding court actions and settlements related to patents. These changes are intended to ensure that FDA is promptly advised of court actions and documented agreements that may affect the timing of approval of a 505(b)(2) application or ANDA for the efficient administration of the FD&C Act. FDA does not have the resources to monitor the numerous court actions that are pending at any given time which may affect the date of approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval.

Table 14 summarizes the proposed changes related to notification of court actions or documented agreements.

Table 14.--Highlights of Proposed Changes Regarding Notification of Court Actions or Documented Agreements¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Notification of court actions (§ 314.107(e))</u></p> <ul style="list-style-type: none"> Applicant must submit a copy of the entry of the order or judgment to the Office of Generic Drugs or to the appropriate division in the Office of New Drugs, as applicable, within 10 working days of a final judgment. 	<p><u>Notification of court actions or documented agreements (§ 314.107(e)(1) and (e)(2))</u></p> <ul style="list-style-type: none"> Applicant must submit the following information to FDA, as applicable: <ul style="list-style-type: none"> --a copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in § 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed, and written notification of whether any such court action has been appealed; --A copy of any order entered by the court terminating the 30-month or 7½-year period described in § 314.107(b)(3)(i) and (b)(3)(ii); --A copy of any documented agreement described in § 314.107(b)(3)(vi); --A copy of any preliminary injunction described in § 314.107(b)(3)(v), and a copy of any subsequent court order lifting the injunction; and --A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in § 314.107(b)(3)). All required information must be sent to the Office of Generic Drugs or to the appropriate division in the Office of New Drugs, as applicable, within 14 days of: <ul style="list-style-type: none"> --the date of entry by the court, --the date of appeal or expiration of the time for appeal, or --the date of documented agreement, as applicable.

¹These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

Proposed § 314.107(e)(1)(i) would require a 505(b)(2) or ANDA applicant to submit a copy of any judgment by the court (district court or mandate of the court of appeals) finding a patent described in § 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed. This proposed requirement imposes a duty on 505(b)(2) and ANDA

applicants to notify FDA regarding any court judgment regardless of whether or not the action for patent infringement has resulted in a substantive determination by the court regarding validity, enforceability, and/or infringement of the patent.

In addition, we are proposing to require 505(b)(2) and ANDA applicants to submit to FDA a copy of certain documented agreements and court actions other than judgments to facilitate FDA's administration of the FD&C Act. Proposed § 314.107(e)(1)(i) would require a 505(b)(2) or ANDA applicant to submit a copy of a settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in proposed § 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed. It should be noted that this proposal would require submission of written documentation that the parties have entered into a settlement that has terminated the patent infringement litigation, but does not require applicants to send copies of the actual settlement agreement to FDA (compare section 1112 of the MMA (requiring that generic drug applicants file certain agreements with the FTC)). Proposed § 314.107(e)(1)(ii) would require a 505(b)(2) or ANDA applicant to submit written notification of whether or not any action by the court described in § 314.107(e)(1)(i) has been appealed within the time permitted for an appeal. Proposed § 314.107(e)(1)(iii) and (e)(1)(iv) would require a 505(b)(2) or ANDA applicant to submit a copy of any order entered by the court terminating the 30-month or 7½-year period described in proposed § 314.107(b)(3)(i) and (b)(3)(ii), and any documented agreement described in proposed § 314.107(b)(3)(vi). Proposed § 314.107(e)(1)(v) would require a 505(b)(2) or ANDA applicant to submit a copy of any preliminary injunction described in § 314.107(b)(3)(v), and a copy of any subsequent court order lifting the injunction. Proposed § 314.107(e)(1)(vi) would require a 505(b)(2) or ANDA applicant to submit a copy of any court

order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in § 314.107(b)(3)). This revision is intended to conform with proposed § 314.107(b)(4) (see section II.M.2.d). These court actions and documented agreements also may affect the timing of approval of a 505(b)(2) application or ANDA and frequently are unpublished. If an applicant is unsure whether a particular court action or documented agreement requires notification to FDA under proposed § 314.107(e), we recommend submission.

We also are proposing to modify the timeframe for a 505(b)(2) or ANDA applicant to submit the required information to the appropriate division in OND or to OGD, as applicable, to ensure timely notification to FDA. Proposed § 314.107(e)(2) would require submission of all required information within 14 calendar days of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written agreement, as applicable. We are proposing to change the timeframe for submission of required information from 10 working days to 14 calendar days for clarity and consistency with other counting conventions used in part 314.

II.M.6. Computation of the 45-Day Time Clock (Proposed § 314.107(f))

We are proposing to revise § 314.107(f) to clarify the computation of the 45-day period after receipt of notice of paragraph IV certification and to enhance the requirements for notifying FDA of any legal action filed within this timeframe. Table 15 summarizes the proposed changes related to the 45-day period after receipt of notice of paragraph IV certification. We seek comment on the proposed notification requirement and alternative ways for FDA to monitor compliance with the FD&C Act.

Table 15.--Highlights of Proposed Changes Regarding the 45-day Period After Receipt of Notice of Paragraph IV Certification¹

Current Regulations	Proposed Revisions to Regulations
<p><u>Computation of 45-day time clock (§ 314.107(f)(1))</u></p> <ul style="list-style-type: none"> The 45-day clock described in § 314.107(b)(3) begins on the day after the date of receipt of the applicant's notice of certification by the patent owner or its representative, and by the approved application holder. 	<p><u>Computation of 45-day time clock (§ 314.107(f)(1))</u></p> <ul style="list-style-type: none"> The 45-day clock described in § 314.107(b)(3) as to each recipient required to receive notice of paragraph IV certification under §§ 314.52 or 314.95 begins on the day after the date of receipt of the applicant's notice of certification by each recipient.
<p><u>Computation of 45-day time clock (§ 314.107(f)(2))</u></p> <ul style="list-style-type: none"> The 505(b)(2) or ANDA applicant must notify FDA immediately of the filing of any legal action filed within 45 days of receipt of the notice of certification. The notification to FDA of the legal action must include, among other things: <ul style="list-style-type: none"> (iv) A certification that an action for patent infringement identified by number, has been filed in an appropriate court on a specified date. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. 	<p><u>Notification of filing of legal action (§ 314.107(f)(2)(i) to (f)(2)(ii))</u></p> <ul style="list-style-type: none"> The 505(b)(2) or ANDA applicant must notify FDA in writing within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of certification by any recipient. The notification to FDA of the legal action must include, among other things: <ul style="list-style-type: none"> (iv) A statement that an action for patent infringement, identified by the court, case number and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date. A patent owner or NDA holder (or their representatives) may also notify FDA of the filing of any legal action for patent infringement.
<p><u>Computation of 45-day time clock (§ 314.107(f)(2))</u></p> <ul style="list-style-type: none"> If the 505(b)(2) or ANDA applicant or the patent owner or its representative does not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the application, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the 505(b)(2) application or ANDA will be made effective immediately upon expiration of the 45 days or upon completion of FDA's review and approval of the application, whichever is later. 	<p><u>Notification of filing of legal action (§ 314.107(f)(2)(iii))</u></p> <ul style="list-style-type: none"> If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or their representatives do not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of FDA's review of the 505(b)(2) application or ANDA, whichever is later.

Table 15.--Highlights of Proposed Changes Regarding the 45-day Period After Receipt of Notice of Paragraph IV Certification¹

Current Regulations	Proposed Revisions to Regulations
<u>Computation of 45-day time clock (§ 314.107(f)(3))</u> <ul style="list-style-type: none"> If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapse, approval of the ANDA or the 505(b)(2) application will be made effective upon completion of FDA's review and approval of the application. FDA will only accept a waiver in the form specified in § 314.107(f)(3)). 	<u>Waiver (§ 314.107(f)(3))</u> <ul style="list-style-type: none"> If the patent owner or NDA holder who is an exclusive patent licensee (or their representatives) waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or NDA holder who is an exclusive patent licensee (or their representatives) submits to FDA a valid waiver before the 45 days elapse, the 505(b)(2) application or ANDA may be approved upon completion of the Agency's review of the application. FDA will only accept a waiver in the form specified in § 314.107(f)(3), as proposed for revision.

¹ These highlights describe important proposed revisions to our regulations, but should not be relied upon in place of the proposed regulation.

We are proposing to revise § 314.107(f)(1) to clarify that the 45-day period after receipt of notice of paragraph IV certification is calculated for each recipient required to be notified under §§ 314.52(a) and 314.95(a). This proposed revision would codify FDA's longstanding interpretation of section 505(b)(3) and (j)(2)(B) of the FD&C Act, as amended by the MMA. This interpretation ensures that each person required to receive notice under § 314.52 or § 314.95, as applicable, also receives the full 45-day period in order to evaluate whether to initiate an action for patent infringement and obtain a 30-month (or 7½-year) stay of approval while litigation is pending. Accordingly, a 505(b)(2) or ANDA applicant's notice of paragraph IV certification may result in more than one "45-day clock" if the NDA holder and patent owners(s) are different entities and receive notice of paragraph IV certification on different days.

Proposed § 314.107(f)(2) would require that a 505(b)(2) or ANDA applicant notify FDA in writing within 14 calendar days of the filing of any legal action filed within 45 days of receipt of the notice of certification. We are proposing to replace the current requirement for "immediate" notification to establish a date certain by which the applicant must send written notification to FDA. This revision is intended to enhance compliance and conform with

proposed § 314.107(e), which would require a 505(b)(2) or ANDA applicant to submit notification of court actions and documented agreements (and a copy of certain court actions) to FDA within 14 calendar days of entry by the court, the date of appeal or expiration of the time for appeal, or the date of documented agreement, as applicable (see section II.M.5).

We also are proposing to revise § 314.107(f)(2)(iv) (redesignated as § 314.107(f)(2)(i)(D)) to eliminate the requirement that the notification to the Agency include a “certification” that an action has been filed. This requirement has resulted in confusion, and the Agency has concluded that a written “statement” containing the necessary information is adequate. We are proposing to require that this statement contain the patent number(s) of the listed patent(s) at issue in the patent infringement action, in addition to the court and case number. The patent number(s) of the listed patent(s) at issue in the litigation will assist FDA in its administration of the approval requirements for 505(b)(2) applications and ANDAs.

We are proposing to expressly state that an NDA holder or its representative also may notify FDA of the filing of any legal action for patent infringement, irrespective of whether the NDA holder is an exclusive patent licensee and initiated the patent infringement action. The notification must be sent to the appropriate office or division and contain the information described in proposed § 314.107(f)(2)(i).

Proposed § 314.107(f)(2)(iii) clarifies that a 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed within the 45-day period) or upon completion of FDA’s review of the 505(b)(2) application or ANDA, whichever is later. This provision would apply, for example, if an applicant changed a paragraph III certification or a statement pursuant to section 505(b)(2)(B) or 505(j)(2)(A)(viii), as applicable, to a paragraph IV

certification during review of the 505(b)(2) application or ANDA and the 45-day period had not elapsed by the time the office or division was ready to take an action on the application. It is unlikely that this provision would be implicated in most cases, however, because a 505(b)(2) or ANDA applicant is required by statute to provide notice of paragraph IV certification not later than 20 days after the date of the postmark on the acknowledgment letter or paragraph IV acknowledgment letter, and review of an application would not be expected to be completed before the 45-day period for each recipient had ended. The proposed revisions to § 314.107(f)(2)(iii) and (f)(3) would replace the current references to the approval of a 505(b)(2) application or ANDA being made effective because this text incorrectly suggests that FDA might issue an approval letter that would become effective at some date in the future (see section II.A.2.dd and II.I). In addition, proposed § 314.107(f)(2)(iii) clarifies that FDA would not approve a 505(b)(2) application or ANDA upon expiration of the 45-day period unless the 505(b)(2) or ANDA applicant had confirmed that a legal action for patent infringement had not been filed.

Proposed § 314.107(f)(3) would permit a representative of the patent owner or NDA holder who is an exclusive patent licensee to waive the opportunity to file a patent infringement action within the 45-day period. This revision is intended to conform with other sections of part 314, including §§ 314.52 and 314.95 which permit notice of paragraph IV certification to be sent to a representative designated by the patent owner to receive notice and the NDA holder's attorney, agent, or other authorized official.

Finally, we are proposing to revise the title to § 314.107(f) and add titles to paragraphs (f)(1), (f)(2), and (f)(3) of that section for administrative convenience.

II.M.7. Conversion of Approval to Tentative Approval (Proposed § 314.107(g))

We are proposing to add § 314.107(g) to clarify that if FDA issues an approval letter in error or a court enters an order requiring that the date of approval be delayed for an already approved 505(b)(2) application or ANDA, FDA will convert the approval to a tentative approval if appropriate.

An approved application may be converted to tentatively approved status if a court determines that a listed patent has been infringed by a 505(b)(2) or ANDA applicant and issues an order pursuant to 35 U.S.C. 271(e)(4) requiring that the effective date of approval shall not be earlier than the date on which the infringed patent will expire, including any pediatric exclusivity that may attach to that patent (see, e.g., Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004)). In addition, FDA will convert an approval to tentatively approved status if the approval letter was issued in error (for example, if an ANDA applicant failed to notify FDA of an adverse decision in patent infringement litigation).

II.N. Assessing Bioavailability and Bioequivalence for Drugs Not Intended To Be Absorbed Into the Bloodstream (Proposed § 320.23)

The MMA amends section 505(j)(8) of the FD&C Act to explicitly authorize FDA to establish methods for assessing bioavailability and bioequivalence for drugs that are not absorbed into the bloodstream (see section 505(j)(8)(A)(ii) and (j)(8)(C) of the FD&C Act). These amendments essentially codify our existing practice of establishing such methods, as reflected in current §§ 320.23(a)(1) and 320.24 and in our implementation of these regulations.

Our proposal would revise the text of § 320.23 to more precisely reflect the text of section 505(j)(8) of the FD&C Act. However, these proposed revisions are not intended to change our current interpretation of § 320.23, as the amendments to section 505(j)(8) of the

FD&C Act are intended to codify our existing interpretation (see section 1103(b) of the MMA, which specifically states that the amendments made to section 505(j)(8) of the FD&C Act “do[] not alter the standards for approval of [ANDAs].”).

II.O. Miscellaneous

II.O.1. Clarifying Revisions and Editorial Changes

We are proposing several clarifying revisions and editorial changes throughout the sections of parts 314 and 320 that are the subject of this rulemaking. These changes are intended to promote consistency throughout our regulations, incorporate “plain language,” employ grammatically correct phrasing, and otherwise clarify the text of these regulations. Examples of proposed revisions that are not otherwise described in this document are provided below.

- Change “means” to “is” after each term described in the definitions section (see proposed § 314.3(b));
- change “shall” to “must” as appropriate (see generally part 314);
- change “are required” to “must” because an applicant is always required to comply with applicable regulations (see proposed § 314.50(d)(5));
- change “prior to the submission of” to “before submitting” for clarity (see proposed § 314.50(d)(5));
- change “claims no uses” to “does not claim a use” to correct grammar (see proposed §§ 314.52(a) and 314.95(a)); and
- change “each amendment to § 314.50(d)(1)” to “each amendment to a section of the NDA described in § 314.50(d)(1)” for clarity (see proposed § 314.60(d)).

In the codified section of this proposed rule, we have indicated proposed editorial changes as amendatory instructions to remove and add text. In some instances, however, it was

necessary to print an entire paragraph to indicate proposed changes that are only editorial changes and would not affect substantive portions of the proposed rule.

We also are proposing to correct statutory citations in part 314 that have changed due to a series of amendments to the FD&C Act (see, e.g., proposed §§ 314.52(c), 314.60(c), and 314.95(c) and (f)).

II.O.2. Effect of Other Rulemaking

In anticipation of the Agency's business process efforts to move all submissions to FDA to electronic submission, we are proposing certain revisions to provisions that clearly contemplate submission of paper to facilitate the transition to electronic submissions and reduce the volume of conforming revisions that may be needed in the future. Examples of these proposed revisions are provided below:

- Change “in a form other than hard copy, for example, on microfiche or computer tapes” to “in an alternate form” to reflect advances in technology and facilitate the transition to electronic submissions (see proposed § 314.50(f)(4));
- delete references to “mailing cover” (see proposed §§ 314.53(d)(6) and 314.70(b)(4)); and
- change “cover letter” to “submission” (see proposed § 314.70(a)(6)).

FDA is committed to adapting its business practices to evolving technology, including using the significant advancements in Web-based, electronic systems. We anticipate that Web-based filing of most submissions eventually will be required. We anticipate that when such a change to an electronic submission system is implemented, future guidance will address any technical questions related to such submissions. Until such time, the sponsor or applicant must submit

them in the manner described in the regulations and to the appropriate FDA location identified in the regulations.

III. Legal Authority

The MMA and sections 505, 505A, 527, and 701 (21 U.S.C. 360cc and 371) of the FD&C Act provide the principal legal authority for this proposed rule. Section 505(b) of the FD&C Act describes the contents of an NDA and 505(b)(2) application, including patent listing and patent certification requirements. Section 505(j) of the FD&C Act describes the contents of an ANDA, including bioequivalence information, patent certification requirements, and criteria for a petitioned ANDA. Section 505(b) and (j) of the FD&C Act restrict certain amendments and supplements to a 505(b)(2) application or an ANDA. Section 505(b), (c), and (j) of the FD&C Act describe the timing of approval for 505(b)(2) applications and ANDAs that are subject to the patent and marketing exclusivity protections accorded the listed drug(s) relied upon and the RLD, respectively. Section 505(j) also describes the availability of 180-day exclusivity for a first ANDA applicant.

Section 505A of the FD&C Act describes the availability of pediatric exclusivity and describes the effect of such exclusivity on approval of 505(b)(2) applications and ANDAs. Section 527 of the FD&C Act describes the effect of orphan exclusivity on approval of 505(b)(2) applications and ANDAs.

Thus, sections 505, 505A, and 527 of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serve as our principal legal authority for this proposal.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We do not believe this proposed rule would result in a significant impact on a substantial number of small entities, but the impacts are uncertain. Because we are uncertain whether the proposed rule would have a significant economic impact on a substantial number of small entities, this and other sections of the preamble and the full preliminary regulatory impact analysis constitute the Agency's regulatory flexibility analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$141 million, using the most current (20132) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

This proposed rule would implement portions of the MMA in a manner that preserves the balance struck in the 1984 Hatch-Waxman Amendments between encouraging the availability of less expensive generic drugs and bringing innovative new drugs to market. This rule would also revise and clarify procedures related to the approval of 505(b)(2) applications and ANDAs to reduce uncertainty among drug firms, reduce costs to industry, and reduce demands on FDA resources responding to industry inquiries.

FDA has been implementing the MMA directly from the statute for several years and based on this experience has identified opportunities to clarify MMA provisions through the adoption of codified language. To the extent that clarified regulatory language improves certainty among regulated entities, this proposal, if promulgated, would reduce industry compliance costs and Agency enforcement costs. The full discussion of economic impacts is available in docket FDA-2011-N-0830 and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>

(Ref. 1).

IV.A. Summary of the Benefits and Costs of the Proposed Rule

Although many provisions of this proposed rule would codify current practice, elements of this proposal would lead to changes that generate additional benefits and costs. This proposed rule would affect applicants and application holders for NDAs (including 505(b)(2) applications) and ANDAs. Provisions of this rule would affect the submission of patent information by NDA holders for listing in the Orange Book and the submission by 505(b)(2) and ANDA applicants of a patent certification or statement addressing the listed patent(s) for the listed drug(s) relied upon or RLD, respectively. This proposed rule would also affect, for those certifying that a listed patent is invalid, unenforceable, or not infringed (paragraph IV certification), the requirements

for the provision of notice of the paragraph IV certification to each patent owner and the NDA holder for the listed drug. The proposed rule would also affect other requirements associated with 505(b)(2) applications and ANDAs.

This proposed rule would revise certain aspects of the regulations on listing of patent information, patent certification requirements, and a 30-month stay of approval. It would also update regulations pertaining to the type of bioavailability and bioequivalence data that can be used to support 505(b)(2) applications and ANDAs. These proposed revisions to the Agency's regulations in parts 314 and 320 would implement portions of Title XI of the MMA and facilitate compliance with and enforcement of the FD&C Act.

We present a summary of benefits and costs in Table 16. The estimated annual monetized benefits of this proposed rule are \$194,314, and estimated annual monetized costs are \$91,371. We have also identified, but are unable to quantify, impacts from proposed changes to submitted patent information and the implementation of an administrative consequence for failing to provide notice within the timeframe specified by the MMA.

Table 16.--Economic Data: Costs and Benefits Statement

[illegible]

Table 16.--Economic Data: Costs and Benefits Statement

Table 10: Economic Data: Costs and Benefits Statement							
				Units			
Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Federal Annualized Monetized \$millions/year					7%		None.
					3%		
From/To	From:			To:			
Other Annualized Monetized \$millions/year					7%		None.
					3%		
From/To	From:			To:			
Effects							
State, Local, or Tribal Government: Not applicable							
Small Business: For firms with 25 to 49 employees, which is a more likely lower bound for firms submitting 505(b)(2) applications, the unit cost of this provision would be less than 0.05 percent of average shipments.							
Wages: No estimated effect							
Growth: No estimated effect							

IV.B. Summary of Regulatory Flexibility Analysis

FDA conducted a regulatory flexibility analysis of the impact of the proposed rule on small entities. Statistics on the classification of firms by employment size from the U.S. Bureau of the Census show that in 2005, at least 85 percent of pharmaceutical manufacturing entities had fewer than 500 employees and would have been considered small by the U.S. Small Business Administration (Ref. 2).

We have provided monetized estimates for \$194,314 in benefits and \$91,371 in costs. These costs of this proposed rule are generally small unit costs incurred across many entities. Our estimated unit costs for all but one item are less than \$190 per unit. In table 17, we express the unit cost of an amendment to a patent certification in terms of hundredths of a percent of average establishment shipments. Excluding one item (505(b)(2) applicants providing a patent certification to a pharmaceutically equivalent drug product), there are costs of \$83,146 attributable to about 1,200 units. Some affected entities would face multiple unit costs of some type in a year, but even this circumstance would not approach a significant impact on a

substantial number of small entities. For a unit cost of \$190 to amount to 1 percent of average shipments among establishment with fewer than 5 employees, the entity would have to incur that cost more than 40 times.

Table 17.--Small Entity Characteristics and the Impact of Unit Costs Attributable to this Proposed Rule

	Pharmaceutical Preparation Manufacturing (NAICS 325412)	
No. of Employees	<5	20-49
Total Value of Shipments (\$1,000)	187,933	978,494
No. of Establishments	228	109
Average Value of Shipments (\$)	824,268	8,977,009
Unit Costs of Identifying a Pharmaceutically Equivalent Drug Product as a Listed Drug Relied Upon per § 314.50(i)(1)(i)(C) as a Percentage of the Average Value of Shipments	0.50%	0.046%

V. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). We describe these provisions below in this section of the document with an estimate of the annual reporting burden. Our estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Revisions to Implement Portions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 and Other Changes.

Description of Respondents: Respondents to this collection of information are NDA applicants (including 505(b)(2) applicants) and ANDA applicants, patent owners, and their representatives.

Burden Estimate: This proposed rule would implement portions of Title XI of the MMA that pertain to a 505(b)(2) or ANDA applicant's provision of notice of paragraph IV certification to each patent owner and the NDA holder; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This proposed rule also would amend certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

FDA currently has OMB approval for the collection of information entitled "Application for Food and Drug Administration Approval to Market a New Drug" (OMB control number 0910-0001). This collection of information includes, among other things:

- The requirements in §§ 314.50(i) and 314.94(a)(12) for submission of an appropriate patent certification or statement in a 505(b)(2) application or ANDA;
- the requirements in §§ 314.52 and 314.95 for a 505(b)(2) or ANDA applicant to send notice of any paragraph IV certification to each patent owner and the NDA holder and amend its 505(b)(2) application or ANDA to certify that notice has been provided and to document receipt of the notice;

- the content requirements in § 314.54 for a 505(b)(2) application;
- the requirements in §§ 314.60 and 314.96 for applicants that amend an unapproved 505(b)(2) application or ANDA, respectively;
- the requirements in §§ 314.70 and 314.97 for supplements submitted to FDA for certain changes to an approved 505(b)(2) application or ANDA;
- the requirements in §§ 314.90 and 314.99 for applicants that request waivers from FDA for compliance with §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively;
- the procedures in § 314.107(c) by which a first applicant notifies FDA of the date of first commercial marketing;
- the requirement in § 314.107(e) for an applicant to submit to FDA a copy of certain court decisions related to a patent that is the subject of a paragraph IV certification;
- the requirement in § 314.107(f) for a 505(b)(2) or ANDA applicant to notify FDA immediately of the filing of any legal action within 45 days of receipt of the notice of paragraph IV certification by each patent owner or the NDA holder; and
- the requirement in § 314.107(f) for a patent owner or NDA holder who is an exclusive patent licensee that waives its opportunity to file a legal action for patent infringement within the 45-day period to submit to FDA a waiver in the specified format.

FDA has OMB approval for the collection of information entitled “General Administrative Procedures: Citizen Petitions; Petition for Reconsideration or Stay of Action; Advisory Opinions” (OMB control number 0910-0183). This collection of information includes, among other things, the requirements in § 314.93 for submitting a suitability petition in accordance with 21 CFR 10.20 and 10.30.

FDA also has received OMB approval for the collection of information entitled “Applications for Food and Drug Administration Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed” (OMB control number 0910-0513). This collection of information includes the requirements in § 314.50(h) for submission of patent information in an NDA, an amendment, or a supplement, as described in § 314.53. Section 314.53 requires that an applicant submitting an NDA, an amendment, or a supplement, except as provided in § 314.53(d)(2), submit on Forms FDA 3542a and 3542 the required patent information described in this section.

We are not reestimating these approved burdens. Only the reporting burdens associated with the MMA’s amendments to the FD&C Act and the proposed changes to parts 314 and 320 are estimated.

Under section 505(b), (c), and (j) of the FD&C Act and this proposed rule, the following information would be submitted to FDA but is not currently approved by OMB under the PRA:

Proposed § 314.50(i)(1)(i)(C) would require a 505(b)(2) applicant to submit an appropriate patent certification or statement for each patent listed in the Orange Book for a drug product(s) that is pharmaceutically equivalent to the proposed drug product for which the 505(b)(2) application is submitted. Proposed § 314.54 would require a 505(b)(2) applicant to identify a pharmaceutically equivalent product as a listed drug relied upon and to comply with applicable regulatory requirements. Generally, 505(b)(2) applications submitted for a proposed drug product for which there is an approved pharmaceutical equivalent already cite the pharmaceutically equivalent product as a listed drug relied upon to support approval. Therefore, we are not estimating a new burden for proposed § 314.54 at this time. Based on our experience

reviewing 505(b)(2) applications, we estimate that proposed § 314.50(i)(1)(i)(C) may result in approximately two instances per year in which an applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon and comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for the pharmaceutically equivalent listed drug relied upon). Based on an estimated average of 2.6 patents by each NDA holder for listing in the Orange Book, we estimate that there will be 5.2 responses per year, and the burden hours associated with this requirement in proposed § 314.50(i)(1)(i)(C) will be approximately 2 hours per response. If the patent certification submitted pursuant to proposed § 314.50(i)(1)(i)(C) is a paragraph IV certification, the applicant also must comply with the requirements in § 314.52 for notice of paragraph IV certification, which add approximately 80 hours (15.33 hours per response) to the currently approved burden hours. This estimate reflects other proposals described in this section of the document that would reduce the currently approved burden for § 314.52 from 16 hours per response to 15 hours per response, and the additional content requirement in proposed § 314.52(c) that would increase the estimated burden by 0.33 hours per response. As previously noted, we are not reestimating approved burdens in this document. Accordingly, the estimate provided for § 314.52(a), (b), (c), and (e) reflects the additional burden that may arise from the requirement in proposed § 314.50(i)(1)(i)(C) if the 505(b)(2) applicant submits a paragraph IV certification. We separately describe and estimate the burden of the additional content requirement in proposed § 314.52(c) for the estimated average of seven 505(b)(2) applications filed per year that contain one or more paragraph IV certification.

Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii) would require a 505(b)(2) or ANDA applicant to amend its patent certification from a paragraph IV certification to a paragraph III

certification after the court enters a final decision from which no appeal has been or can be taken, or signs a settlement order or consent decree with a finding of infringement (unless the patent also is found invalid). Proposed §§ 314.50(i)(6) and 314.94(a)(12)(viii) also would require a 505(b)(2) or ANDA applicant to submit an amended patent certification in certain circumstances after the NDA holder has requested to remove a patent or patent information from the list. Based on our experience and review of selected court decisions, we estimate that there are approximately 12 instances per year in which a party has submitted a court decision or order with a finding of infringement. In addition, there are approximately 24 instances per year in which the NDA holder has requested to remove a patent or patent information from the list and the patent or patent information has been removed. Based on our experience, we estimate that this requirement may result in approximately 36 and 108 instances per year in which an applicant amends its 505(b)(2) application or ANDA, respectively, to submit a revised patent certification, and the burden hours associated with this requirement will be approximately 2 hours per response. Proposed §§ 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(vi)(C)(1)(ii) would expressly codify the current requirement for a 505(b)(2) or ANDA applicant to submit a patent certification or statement if, after submission of the application, a new patent is issued by the PTO that in the opinion of the applicant and to the best of its knowledge, claims the listed drug or an approved use for such listed drug and for which information is required to be filed by the NDA holder. The burden hours associated with compliance with current provisions of §§ 314.50(i)(1) through (i)(6) and 314.94(a)(12)(i) through (a)(12)(viii) are described in the burden hours estimate currently approved under OMB control number 0910-0001.

Proposed §§ 314.52(a) and 314.95(a) would expand the list of acceptable delivery methods that may be used to send notice of paragraph IV certification to the NDA holder and

each patent owner, and thereby reduce the burden on applicants to submit, under current §§ 314.52(a) and (e), a request to FDA to use common alternate delivery methods. We receive approximately 205 written inquiries per year from 505(b)(2) or ANDA applicants requesting permission to send notice of paragraph IV certification by an overnight delivery service.

Proposed §§ 314.52(a) and 314.95(a) would eliminate the requirement to submit a request to use a designated delivery service, as defined in proposed §§ 314.52(f) and 314.95(f). We estimate that approximately 95 percent of these written inquiries will no longer be required because the alternate delivery method would fall within the definition of a “designated delivery service” in proposed §§ 314.52(g) and 314.95(g).

Proposed §§ 314.52(c) and 314.95(c) would require that notice of paragraph IV certification contain a statement that the applicant has received the acknowledgment letter or the paragraph IV acknowledgment letter, as applicable. In addition, proposed § 314.52(c) would require that the notice of paragraph IV certification contain a statement that a 505(b)(2) application that contains any required bioavailability or bioequivalence data has been submitted by the applicant and filed by FDA, as required by section 505(b)(3)(D)(i) of the FD&C Act. We estimate that these additional content requirements for the notice of paragraph IV certification would increase the burden of providing notice of paragraph IV certification by approximately 20 minutes. Based on an estimated average of 7 505(b)(2) applications filed per year that contain one or more paragraph IV certifications and 209 ANDAs received per year that contain one or more paragraph IV certifications, we estimate that there will be 21 and 627 responses per year, and the burden hours associated with this requirement will be approximately 20 minutes per response.

Proposed §§ 314.52(d)(1) and 314.95(d)(1) would require notice of paragraph IV certification regardless of whether notice has already been provided for another paragraph IV certification contained in the 505(b)(2) application or ANDA or an amendment or supplement to the 505(b)(2) application or ANDA, as required by section 505(b)(3)(B)(ii) and (j)(2)(B)(ii)(II) of the FD&C Act. Since enactment of the MMA, FDA has regulated directly from the statute and required notice of paragraph IV certification in these circumstances. Thus, the burden associated with this statutory requirement is reflected in the burden hours estimate for §§ 314.52 and 314.95 currently approved under OMB control number 0910-0001.

Proposed §§ 314.52(e) and 314.95(e) would permit a 505(b)(2) or ANDA applicant to submit a single amendment containing documentation of timely sending and receipt of notice of paragraph IV certification. Currently, an applicant is required to amend its 505(b)(2) application or ANDA both at the time of sending notice of paragraph IV certification and after the notice was received by each patent owner and the NDA holder (see current §§ 314.52(b) and (e) and 314.95(b) and (e)). Proposed § 314.95(e) also would require an ANDA applicant to include in its amendment a dated printout of the Orange Book entry for the RLD. FDA has OMB approval for the burden hours estimate of 16 hours per response for the estimated 260 responses submitted annually to comply with §§ 314.52 and 314.95 (see OMB control number 0910-0001). We estimate that 2 hours of the 16 hours per response are attributable to compliance with current §§ 314.52(b) and (e) and 314.95(b) and (e). We estimate that the burden hours associated with the requirement in proposed §§ 314.52(e) and 314.95(e) (including submission of the dated printout of the Orange Book entry) would be approximately 1 hour per response for each of the estimated 7 and 209 responses per year by our updated estimate of 7 505(b)(2) applicants and 209 ANDA applicants whose applications were filed or received, as applicable, by FDA and

contained one or more paragraph IV certifications. Therefore, the proposal would reduce the currently approved burden for §§ 314.52 and 314.95 by 1 hour.

Proposed § 314.53(c)(2) would decrease the patent information that NDA applicants are currently required to submit for listing in the Orange Book. Proposed § 314.53(c)(2) would require an NDA applicant to submit information on a previously submitted patent only if a patent is a reissued patent of a patent previously submitted for listing for the NDA or supplement. Proposed § 314.53(c)(2) would require submission of patent information on whether a drug substance patent claims a polymorph only if such patent claims only a polymorph that is the same active ingredient described in the NDA or supplement. Proposed § 314.53(c)(2) also would provide that an applicant that submits information for a patent that claims either the drug substance or drug product and meets the requirements for patent listing on that basis is not required to provide information on whether that patent also claims the drug product or drug substance, respectively. The information collection resulting from current § 314.50(h) (citing § 314.53) and Form FDA 3542a has been approved by OMB under control number 0910-0153 for FDA's estimate of 20 hours per response. We estimate the proposed revisions to our regulations will reduce the time needed to complete Form FDA 3542a by approximately 3 hours per response.

Proposed § 314.53(d)(2) would enable FDA to reduce duplicative submission of patent information and require such information only for a supplement to change the dosage form or route of administration, to change the strength, to change the drug product from prescription to OTC use, or to correct previously submitted patent information that differently or no longer claims the changed product.

Proposed § 314.53(f)(2) would expressly require correction or change of patent information if the NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, if the NDA holder is required by court order to amend patent information or withdraw a patent from the list, or if the term of a listed patent is extended under 35 U.S.C. 156(e). We estimate that these corrections and changes of patent information would result in approximately 62 submissions of Form FDA 3542 or other written submission, as provided in proposed § 314.53(f)(2)(iv), by approximately 39 NDA holders. We further estimate that the burden hours associated with the requirement in proposed § 314.53(f)(2) would be approximately 1 hour per response.

Section 505(b)(4)(A) and (j)(2)(D)(i) of the FD&C Act generally prohibit the submission of certain types of changes in an amendment or a supplement to a 505(b)(2) application or an ANDA, respectively. Proposed §§ 314.60(e) and 314.70(h) would prohibit an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient, different route of administration, different dosage form, or certain differences in excipients that the drug proposed in the original submission of the 505(b)(2) application. These changes must be requested in a new 505(b)(2) application. This proposed requirement conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see *Separate Marketing Application Guidance*). Accordingly, the burden associated with this statutory requirement is reflected in the burden hours estimate for §§ 314.50 and 314.94 currently approved under OMB control number 0910-0001 for 505(b)(2) applications and ANDAs, respectively.

Proposed §§ 314.60(f), 314.70(i), 314.96(d), and 314.97(c) would require an applicant to submit a patent certification if approval is sought for either of the following types of amendments or supplements to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use or (2) to add a new strength. Proposed §§ 314.60(f) and 314.96(d) also would require an applicant to submit a patent certification if approval is sought for either of the following types of amendments to a 505(b)(2) application or ANDA: (1) To make other than minor changes in product formulation or (2) to change the physical form or crystalline structure of the active ingredient. Although currently the submission of a patent certification is required if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement, as amended (thus the burden hours are currently approved under OMB control number 0910-0001), the patent certification requirements would be broadened under this proposed rule. We estimate that this requirement may result in approximately six and four instances per year in which an applicant is required to submit a patent certification with an amendment or supplement, respectively, to its 505(b)(2) application. We further estimate that this requirement may result in approximately 95 and 16 instances per year in which an applicant is required to submit a patent certification with an amendment or supplement, respectively, to its ANDA. The burden hours associated with these requirements are estimated to be approximately 2 hours per response.

Proposed §§ 314.96(c) and 314.97(b) would prohibit an ANDA applicant from amending or supplementing an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA. An applicant must submit a change of the RLD in a new ANDA. We estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting an amendment for a change of the RLD. We also

estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting a supplement for a change of the RLD. We further estimate that the burden of submitting an ANDA and complying with applicable regulatory requirements, including any required study to demonstrate bioequivalence to the new RLD, will be approximately 288 hours for each of the estimated two responses per year.

Proposed § 314.107(e) would expand the scope of the court actions and documented agreements related to a patent described in § 314.107(b)(3) that are required to be submitted to FDA. Proposed § 314.107(e) also would require submission of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified. FDA has OMB approval for the burden hours estimate of 30 minutes per response for the estimated 98 responses submitted annually by 25 505(b)(2) or ANDA applicants to comply with § 314.107(e) (see OMB control number 0910-0001). Based on our experience, we estimate that 140 505(b)(2) and ANDA applicants will be required to submit a copy of a court action, documented agreement, or written notification of appeal in approximately 310 instances per year. We continue to estimate that the burden associated with submitting a copy of these documents to FDA is approximately 30 minutes per response.

The estimated burden of the burden of this collection of information is described in table 18.

Table 18.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Hours
314.50(i)(1)	2	2.6	5.2	2	10.4
314.50(i)(6)	36	1	36	2	72
314.52(a), (b), (c), and (e)	2	2.6	5.2	15.33	79.7
314.52(c)	7	3	21	0.33 (20 minutes)	7
314.53(f)	39	1.5	62	1	62
314.60(f)	6	1	6	2	12

Table 18.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Hours
314.70(i)	4	1	4	2	8
314.94(a)(12)	108	1	108	2	216
314.95(c)	209	3	627	0.33 (20 minutes)	209
314.96(c)	1	1	1	288	288
314.96(d)	95	1	95	2	190
314.97(b)	1	1	1	288	288
314.97(c)	16	1	16	2	32
314.107(e)	140	2.2	310	0.5 (30 minutes)	155
Total Reporting Burden Hours			1629.1		

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

We have submitted the information collection requirements of this rule to OMB for review. Interested persons are requested to send comments regarding information collection to the Office of Information and Regulatory Affairs, OMB (see ADDRESSES).

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) and 25.31(a) and (g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Effective Date

FDA proposes that any final rule based on this proposal become effective 60 days after publication in the Federal Register.

We intend to apply this rule, if finalized, to any new submission received by FDA on or after the effective date. This proposed rule provides sufficient notice to all interested parties, including NDA holders, NDA applicants (including 505(b)(2) applicants), and ANDA applicants

to adjust their submissions and actions by the time we issue any final rule. However, we invite comments on how a final rule should be implemented.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

X. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not

responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Rule, available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

2. U.S. Department of Commerce, Bureau of the Census, Economic Census, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, Table 4, EC02-311-325412 (RV), 2002.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR parts 314 and 320 as follows:

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 360cc, 371, 374, 379e.

2. Section 314.3 is revised to read as follows:

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

180-day exclusivity period is the 180-day period beginning on the date of the first commercial marketing of the drug (including the commercial marketing of the reference listed drug) by any first applicant. The 180-day period ends on the day before the date on which an ANDA submitted by an applicant other than a first applicant could be approved.

Abbreviated application, abbreviated new drug application, or ANDA is the application described under § 314.94, including all amendments and supplements to the application.

Acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA is sufficiently complete to permit a substantive review. An acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

Act is the Federal Food, Drug, and Cosmetic Act (section 201 et seq. (21 U.S.C. 301 et seq.)).

Active ingredient is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

ANDA holder is the applicant that owns an approved ANDA.

Applicant is any person who submits an NDA (including a 505(b)(2) application) or ANDA or an amendment or supplement to an NDA or ANDA under this part to obtain FDA approval of a new drug and any person who owns an approved NDA (including a 505(b)(2) application) or ANDA.

Application, new drug application, or NDA is the application described under § 314.50, including all amendments and supplements to the application. An NDA refers to “stand-alone” applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

505(b)(2) application is an NDA submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a drug for which the investigations described in section 505(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and relied upon by the applicant for approval of the NDA were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Approval letter is a written communication to an applicant from FDA approving an NDA or an ANDA.

Assess the effects of the change is to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Authorized generic drug is a listed drug, as defined in this section, that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and is marketed, sold, or distributed directly or indirectly to the retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug.

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid

measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence requirement is a requirement imposed by FDA for in vitro and/or in vivo testing of specified drug products that must be satisfied as a condition of marketing.

Class 1 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that contains one or more of the following: Final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform postmarketing studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

Class 2 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that includes any item not specified in the definition of “Class 1 resubmission,” including any item that would require presentation to an advisory committee.

Commercial marketing is the introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA, outside the control of the ANDA holder, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale to parties identified in the approved ANDA.

Complete response letter is a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an NDA or ANDA that must be satisfactorily addressed before it can be approved.

Component is any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

Date of approval is the date on the approval letter from FDA stating that the NDA or ANDA is approved. “Date of approval” refers only to a final approval and not to a tentative approval.

Dosage form is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

- (1) The physical appearance of the drug product,
- (2) The physical form of the drug product prior to dispensing to the patient,
- (3) The way the product is administered, and
- (4) The design features that affect frequency of dosing.

Drug product is a finished dosage form, e.g., tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

Efficacy supplement is a supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling:

- (1) Add or modify an indication or claim;
- (2) Revise the dose or dose regimen;
- (3) Provide for a new route of administration;
- (4) Make a comparative efficacy claim naming another drug product;
- (5) Significantly alter the intended patient population;
- (6) Change the marketing status from prescription to over-the-counter use;

(7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of part 314; or

(8) Incorporate other information based on at least one adequate and well-controlled clinical study.

FDA is the Food and Drug Administration.

First applicant is an applicant that, on the first day on which a substantially complete ANDA containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug.

Inactive ingredient is any component other than an active ingredient.

Listed drug is a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. A drug product is deemed to be a listed drug on the date of the approval letter for the NDA or ANDA for that drug product.

NDA holder is the applicant that owns an approved NDA.

Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g.,

meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

Original application, original NDA is a pending NDA for which FDA has never issued a complete response letter or approval letter, or an NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

Paragraph IV acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review. A paragraph IV acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

Paragraph IV certification is a patent certification of invalidity, unenforceability, or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

Patent owner is the owner of the patent for which information is submitted for an NDA.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical

dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Postmark is an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the U.S. Postal Service or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the U.S. Postal Service or by a designated delivery service. For postmarks documenting an electronic event, the date of transmission is the date (in a particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender's time zone that provides the controlling date of electronic transmission.

Reference listed drug is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

Reference standard is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.

Resubmission is submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An NDA or ANDA for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

Same drug product formulation is the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the Agency's determination of bioequivalence.

Specification is the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved NDA or ANDA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

Strength is the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:

(1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.

(ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or

(2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures

described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).

Substantially complete application is an ANDA that on its face is sufficiently complete to permit a substantive review and contains all the information required under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act and § 314.94.

Tentative approval is notification that an NDA or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act, or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the application may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA.

The list is the list of approved drug products published in FDA's current "Approved Drug Products With Therapeutic Equivalence Evaluations," available electronically on FDA's Web site at <http://www.fda.gov/cder>.

Therapeutic equivalents are approved drug products that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected

to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

3. Section 314.50 is amended by:

a. Removing from paragraph (a) introductory text, paragraphs (a)(5), (d)(1)(v), (d)(5)(v), and (d)(5)(vi)(a), paragraph (e)(2) introductory text, and paragraphs (f)(3), (g)(2), and (k) the word “shall” each time it appears and adding in its place the word “must”;

b. Removing from paragraphs (a)(5), (b), (c)(1), (c)(2)(i), and (c)(2)(iv) through (c)(2)(viii), paragraph (d) introductory text, paragraphs (d)(1)(i), (d)(1)(ii)(a), (d)(1)(iii) through (d)(1)(v), (d)(3)(ii), and (d)(5)(iv), paragraph (e)(1)(i) introductory text, paragraph (e)(2), paragraph (f) introductory text, paragraphs (f)(1) through (f)(3), (g)(2), (j)(4)(i), (j)(4)(ii), and (k), paragraph (l) heading, paragraph (l)(1) introductory text, and paragraphs (l)(2) and (l)(4) the word “application” each time it appears and adding in its place “NDA”;

c. Removing from paragraph (j) introductory text the word “shall” and adding in its place the word “must” and removing the phrase “new drug application” and adding in its place “NDA”; and

d. Revising the section heading and section introductory text, paragraphs (a)(1) and (d)(5)(vi)(b), paragraph (e)(1) introductory text, paragraphs (f)(4), (g)(3), and (i), paragraph (j)(4) introductory text, the first two sentences of paragraph (j)(4)(iii), and paragraph (l)(3).

The revisions read as follows:

§ 314.50 Content and format of an NDA.

NDA's and supplements to approved NDA's are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the NDA are required: An archival copy, a review copy, and a field copy. An

NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an NDA of the type described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, an amendment, and a supplement. The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of NDAs to assist applicants in their preparation.

(a) * * *

(1) The name and address of the applicant; the date of the NDA; the NDA number if previously issued (for example, if the NDA is a resubmission or an amendment or supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all INDs (as defined in § 312.3(b) of this chapter) that are referenced in the NDA; the identification numbers of all drug master files and other applications under this part that are referenced in the NDA; and the drug product's proposed indications for use.

* * * * *

(d) * * *

(5) * * *

(vi) * * *

(b) The applicant must, under section 505(i) of the Federal Food, Drug, and Cosmetic Act, update periodically its pending NDA with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These “safety update reports” must include the same kinds of information (from clinical studies, animal studies, and other sources) and must be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports must include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant must submit these reports:

- (1) 4 months after the initial submission;
- (2) In a resubmission following receipt of a complete response letter; and
- (3) At other times as requested by FDA. Before submitting the first such report,

applicants are encouraged to consult with FDA regarding further details on its form and content.

* * * *

(e) * * * (1) Upon request from FDA, the applicant must submit the samples described below to the places identified in the Agency’s request. FDA generally will ask applicants to submit samples directly to two or more Agency laboratories that will perform all necessary tests on the samples and validate the applicant’s analytical procedures.

* * * *

(f) * * *

(4) Applicants are invited to meet with FDA before submitting an NDA to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in an alternate form.

(g) * * *

(3) If an applicant who submits an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act obtains a “right of reference or use,” as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, the applicant must include in its NDA a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its NDA, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its NDA.

* * * * *

(i) Patent certification--(1) Contents. A 505(b)(2) application is required to contain the following:

(i) Patents claiming drug substance, drug product, or method of use. (A) A certification with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the drug substance or drug product on which investigations that are relied upon by the applicant for approval of its 505(b)(2) application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification “Paragraph I Certification”;

(2) That the patent has expired. The applicant must entitle such a certification “Paragraph II Certification”;

(3) The date on which the patent will expire. The applicant must entitle such a certification “Paragraph III Certification”; or

(4) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. The applicant must entitle such a certification “Paragraph IV Certification”. This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. _____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this 505(b)(2) application is submitted.

The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the holder of the approved NDA for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(b) with respect to sending the notice and under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(C) If, before the date of submission of the 505(b)(2) application, there is an approved drug product that is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted, an appropriate patent certification under this section with respect to each patent that claims the drug substance or drug product or that claims an approved use for such drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

(iii) Method-of-use patent. (A) If information that is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 is for a method-of-use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications or other conditions of use that are covered by the use patent, a statement explaining that the method-of-use patent does not claim any of the proposed indications or other conditions of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, the applicant must submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) [Reserved]

(3) Licensing agreements. If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a certification under paragraph (i)(1)(i)(A)(4) of this section (“Paragraph IV Certification”) as to that patent and a statement that it has been granted a patent license. If the patent owner consents to approval of the 505(b)(2) application (if otherwise justified) as of a specific date, the 505(b)(2) application must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the 505(b)(2) application as of a specific date.

(4) Untimely filing of patent information. If a patent described in paragraph (i)(1)(i) of this section is issued and the holder of the approved NDA for the patented drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification is not required to submit an amended certification to address the patent that is late-listed with respect to the pending 505(b)(2) application. Except as provided in § 314.53(f)(1), an NDA holder’s amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if:

(i) The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or

(ii) The amendment is submitted more than 30 days after a corresponding change in approved product labeling. An applicant whose 505(b)(2) application is filed after the NDA holder’s untimely filing of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the patent submission

must submit a certification under paragraph (i)(1)(i) of this section or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) Disputed patent information. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant must submit an appropriate certification for each relevant patent.

(6) Amended certifications. A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the approval of the 505(b)(2) application. An applicant must submit an amended certification as an amendment to a pending 505(b)(2) application. If an applicant with a pending 505(b)(2) application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment for the change in certification has been submitted, the 505(b)(2) application will no longer be considered to be one containing the prior certification.

(i) After finding of infringement. An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (i)(1)(iii) of this

section if the applicant amends its 505(b)(2) application such that the applicant is no longer seeking approval for a method of use claimed by the patent.

(ii) After request to remove a patent or patent information from the list. If the list reflects that an NDA holder has requested that a patent be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will be removed and any applicant with a pending 505(b)(2) application (including a tentatively approved 505(b)(2) application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent shall remain listed until any 180-day exclusivity is extinguished. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. Once an amendment to withdraw the certification has been submitted, the 505(b)(2) application will no longer be considered to be one containing a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application, the applicant must submit an amended certification reflecting that there are no listed patents.

(iii) Other amendments. (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section:

(1) An applicant must amend a submitted certification if, at any time before the approval of the 505(b)(2) application, the applicant learns that the submitted certification is no longer accurate; and

(2) An applicant must submit a certification or statement under paragraph (i)(1) of this section if, after submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a listed drug relied upon or that claims an approved use for such listed drug for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

(B) An applicant is not required to submit a supplement to change a submitted certification when information on an otherwise applicable patent is submitted after the approval of the 505(b)(2) application, except as provided in § 314.70(i).

(j) * * *

(4) If the applicant claims exclusivity under § 314.108(b)(4) or (b)(5), the following information to show that the NDA contains “new clinical investigations” that are “essential to approval of the application or supplement” and “were conducted or sponsored by the applicant”:

* * * *

(iii) * * * If the applicant was the sponsor named in the Form FDA 1571 for an IND under which the new clinical investigation(s) that is essential to the approval of its NDA was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its NDA, and information supporting the certification. * * *

* * * *

(1) * * *

(3) Field copy. The applicant must submit a field copy of the NDA that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the NDA.

* * * *

4. Section 314.52 is revised to read as follows:

§ 314.52 Notice of certification of invalidity or noninfringement of a patent.

(a) Notice of certification. For each patent that claims the listed drug or drugs relied upon or that claims a use for such listed drug or drugs and for which the applicant submits a paragraph IV certification, the applicant must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of business within the U.S., the NDA holder's attorney, agent, or other

authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained from the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855.

(3) This paragraph does not apply to a use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) Sending the notice. (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date it receives a paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the applicant's receipt of a paragraph IV acknowledgment letter. The applicant will not have complied with this paragraph until it sends valid notice.

(3) At the same time it sends the notice required by paragraph (a) of this section, the applicant must submit to FDA an amendment to its 505(b)(2) application that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) Content of a notice. In the notice, the applicant must cite section 505(b)(3)(D) of the Federal Food, Drug, and Cosmetic Act and must include, but is not limited to, the following information:

(1) A statement that a 505(b)(2) application that contains any required bioavailability or bioequivalence studies has been submitted by the applicant and filed by FDA.

(2) The NDA number.

(3) A statement that the applicant has received the paragraph IV acknowledgment letter for the 505(b)(2) application.

(4) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(5) The active ingredient, strength, and dosage form of the proposed drug product.

(6) The patent number and expiration date of each patent on the list alleged to be invalid, unenforceable, or not infringed.

(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(8) If the applicant alleges that the patent will not be infringed and the applicant may later decide to file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied

by an offer of confidential access to the 505(b)(2) application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) Amendment or supplement to a 505(b)(2) application. (1) If, after receipt of an acknowledgment letter or paragraph IV acknowledgment letter, an applicant submits an amendment or supplement to its 505(b)(2) application that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the 505(b)(2) application is submitted to FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the 505(b)(2) application or in an amendment or supplement to the 505(b)(2) application.

(2) If, before receipt of a paragraph IV acknowledgment letter, an applicant submits a paragraph IV certification in an amendment, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraphs (d)(1) or (d)(2) of this section, as applicable.

(e) Documentation of timely sending and receipt of notice. The applicant must amend its 505(b)(2) application to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be

submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or paragraph (d) of this section, as applicable. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, a signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) Approval. If the requirements of this section are met, the Agency will presume the notice to be complete and sufficient and will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved NDA holder as the first day of the 45-day period provided for in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant amends its 505(b)(2) application with a written statement that a later date should be used, count from such later date.

(g) Designated delivery services. (1) For purposes of this section, the term "designated delivery service" is any delivery service provided by a trade or business that the Agency determines:

(i) Is available to the general public throughout the United States;

(ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and

(iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA will periodically issue guidance regarding designated delivery services that meet these criteria.

5. Section 314.53 is revised to read as follows:

§ 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA an NDA or an amendment to it under section 505(b) of the Federal Food, Drug, and Cosmetic Act and § 314.50 or a supplement to an approved NDA under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted and patents for which information must not be submitted--(1) General requirements. An applicant described in paragraph (a) of this section must submit the required information, on the required FDA declaration form, set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant must submit information only on those patents that claim the drug substance that is the subject of the pending or approved NDA or that claim a drug substance that is the same as

the active ingredient that is the subject of the approved or pending NDA. For patents that claim only a polymorph that is the same as the active ingredient described in the approved or pending NDA, the applicant must certify in the required FDA declaration form that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. For patents that claim a drug product, the applicant must submit information only on those patents that claim a drug product, as is defined in § 314.3, that is described in the pending or approved application. For patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA. The applicant must separately identify each pending or approved method of use and related patent claim(s). For approved NDAs, the applicant submitting the method-of-use patent must identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted. If the scope of the method-of-use claim(s) of the patent does not cover every use of the drug, the applicant must only identify the specific portion(s) of the indication or other condition of use claimed by the patent. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) Test data for submission of patent information for patents that claim only a polymorph. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging;

and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

(c) Reporting requirements--(1) General requirements. An applicant described in paragraph (a) of this section must submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is submitted on the appropriate form, Form FDA 3542 or 3542a, and contains the information required in paragraph (c)(2) of

this section. These forms may be obtained on the Internet at <http://www.fda.gov> by searching for “forms”.

(2) Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents--(i) Original declaration. For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant must submit Form FDA 3542a. The following information and verification is required, subject to the exceptions listed in paragraph (c)(2)(i)(S) of this section:

- (A) NDA number;
- (B) Name of NDA sponsor;
- (C) Trade name (or proposed trade name) of new drug;
- (D) Active ingredient(s) of new drug;
- (E) Strength(s) of new drug;
- (F) Dosage form of new drug;
- (G) U.S. patent number, issue date, and expiration date of patent submitted;
- (H) The patent owner's name, full address, phone number and, if available, fax number and email address;
- (I) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);
- (J) Information on whether the patent is a reissued patent of a patent submitted previously for listing for the NDA or supplement;

(K) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the NDA or supplement;

(2) Whether the patent claims only a polymorph that is the same active ingredient that is described in the pending NDA or supplement;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the NDA or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent, including the following:

(1) Whether the patent claims one or more methods of using the drug product for which use approval is being sought and a description of each pending method of use or related indication and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted (if the scope of the method-of-use claim(s) of the patent does not cover every use of the drug, the applicant must only identify the specific portion(s) of the indication or other condition of use claimed by the patent); and

(3) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(i)(M) or (c)(2)(i)(N) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.;

and

(R) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address.

(S) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(i)(M) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(N) of this section on whether that patent also claims the drug product (composition/formulation).

(2) If an applicant submits the information described in paragraph (c)(2)(i)(N) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(M) of this section on whether that patent also claims the drug substance (active ingredient).

(ii) Submission of patent information upon and after approval. Within 30 days after the date of approval of its NDA or supplement, the applicant must submit Form FDA 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will rely only on the information submitted on this form and will not list or publish patent information if the patent declaration is incomplete or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the NDA as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(3) of this section, to be timely filed, patent information for patents issued after the date of approval of the NDA must be submitted to FDA within 30 days of

the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required, subject to the exceptions listed in paragraph (c)(2)(ii)(T) of this section:

- (A) NDA number;
- (B) Name of NDA sponsor;
- (C) Trade name of new drug;
- (D) Active ingredient(s) of new drug;
- (E) Strength(s) of new drug;
- (F) Dosage form of new drug;
- (G) Approval date of NDA or supplement;
- (H) U.S. patent number, issue date, and expiration date of patent submitted;
- (I) The patent owner's name, full address, phone number and, if available, fax number and email address;
- (J) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);
- (K) Information on whether the patent is a reissued patent of a patent submitted previously for listing for the NDA or supplement;

(L) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the approved NDA;

(2) Whether the patent claims only a polymorph that is the same as the active ingredient that is described in the approved NDA;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the approved NDA and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the approved drug product as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent, including the following:

(1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted (if the scope of the method-of-use claim(s) of the patent does not cover every use of the drug, the applicant must only identify the specific portion(s) of the indication or other condition of use claimed by the patent);

(3) The description of the patented method of use as required for publication (which must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval; for example, if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, then the description of the patented method of use must contain only the specific portion(s) of the indication or other method of use claimed by the patent); and

(4) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(ii)(N) or (c)(2)(ii)(O) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition), or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement approved under

section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.;

and

(S) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address.

(T) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(ii)(N) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(O) of this section on whether that patent also claims the drug product (composition/formulation).

(2) If an applicant submits the information described in paragraph (c)(2)(ii)(O) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(N) of this section on whether that patent also claims the drug substance (active ingredient).

(3) No relevant patents. If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner

of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate forms, Form FDA 3542 or 3542a.

(4) Authorized signature. The declarations required by this section must be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) When and where to submit patent information--(1) Original NDA. An applicant must submit with its original NDA submitted under this part, including a 505(b)(2) application, the information described in paragraph (c) of this section on each drug substance (ingredient), drug product (formulation and composition), and method-of-use patent issued before the NDA is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the NDA is filed with FDA but before the NDA is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the NDA under § 314.60.

(2) Supplements. (i) An applicant must submit patent information required under paragraph (c) of this section for a patent that claims the drug substance, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the dosage form or route of administration;

(B) To change the strength; or

(C) To change the drug product from prescription use to over-the-counter use.

(ii) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section (for example, to change the formulation, to add a new indication or other condition of use, or to make any other patented change regarding the

drug substance, drug product, or any method of use), the following patent information submission requirements apply:

(A) If existing patents for which information has already been submitted to FDA for the product approved in the original NDA claim the changed product, the applicant is not required to resubmit this patent information unless the description of the patented method of use would change upon approval of the supplement, and FDA will continue to list this patent information for the product;

(B) If one or more existing patents for which information has already been submitted to FDA no longer claim the changed product, the applicant must submit a request to remove that patent information from the list at the time of approval of the supplement;

(C) If one or more existing drug substance (active ingredient), drug product (formulation and composition), or method-of-use patents claim the changed product for which approval is sought in the supplement and such patent information has not been submitted to FDA, the applicant must submit the patent information required under paragraph (c) of this section.

(3) Newly issued patents. If a patent is issued for a drug substance, drug product, or method of use after an NDA is approved, the applicant must submit to FDA, as described in paragraph (d)(4) of this section, the required patent information within 30 days of the date of issuance of the patent. If the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications will be governed by the provisions regarding untimely filed patents at §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii).

(4) Submission of Forms FDA 3542a and 3542.

(i) Patent information submitted with the filing of an NDA, amendment, or supplement.

The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(i) of this section and § 314.50(h) or § 314.70(f) on Form FDA 3542a to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. Form FDA 3542a should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(ii) Patent information submitted upon and after approval of an NDA or supplement. The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(ii) of this section on Form FDA 3542 to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855.

(5) Submission date. Patent information will be considered to be submitted to FDA for purposes of paragraph (d)(3) of this section as of the earlier of the date the information submitted on Form FDA 3542 is date-stamped by the Office of Generic Drugs, Document Room, or officially received electronically by FDA through the Electronic Submissions Gateway.

(6) Identification. Each submission of patent information, except information submitted with an original NDA, must bear prominent identification as to its contents, i.e., “Patent Information,” or, if submitted after approval of an NDA, “Time-Sensitive Patent Information.”

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the NDA, or, if the patent information is submitted by the applicant after approval of an NDA as provided under paragraph

(d)(2) of this section, as soon as possible after the submission to the Agency of the patent information. A request for copies of the submitted patent information must be sent in writing to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857. This information, and requests for delisting patents, will be subject to public disclosure.

(f) Correction or change of patent information--(1) Requests by persons other than the NDA holder. If any person disputes the accuracy or relevance of patent information submitted to the Agency under this section and published by FDA in the list, or believes that an NDA holder has failed to submit required patent information, that person must first notify the Agency in a written or electronic communication titled “314.53(f) Patent Listing Dispute” that states the grounds for disagreement. Such notification should be directed to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855. The Agency will then request of the applicable NDA holder that the correctness of the patent information or omission of patent information be confirmed within 30 days. For listed patents that claim an approved method of using the drug product, FDA will request that the NDA holder confirm the correctness of its description of the approved indication or method of use that has been included as the “Use Code” in the Orange Book, and provide information on the specific approved use claimed by the patent that enables the Agency to make a determination in accordance with section 505(b)(2)(B) or 505(j)(2)(C)(viii) of the Federal Food, Drug, and Cosmetic Act. Unless the NDA holder withdraws or amends its patent information in response to FDA’s request, the Agency will not change the patent information in the list. If the NDA holder does not change the patent information submitted to FDA, a 505(b)(2) application or an ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act submitted for a drug

that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent. However, if there is insufficient information to make a determination in accordance with section 505(b)(2)(B) or 505(j)(2)(C)(viii) of the Federal Food, Drug, and Cosmetic Act, and the NDA holder has confirmed the correctness of its description of the specific approved use claimed by the patent, the Agency will review the proposed labeling for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.

(2) Requests by the NDA holder.--(i) Patents or patent claims that no longer meet the statutory requirements for listing. If the NDA holder determines that a patent or patent claim no longer meets the requirements for listing in section 505(b)(1) or 505(c)(2) of the Federal Food, Drug, and Cosmetic Act (including if there has been a judicial finding of invalidity for a listed patent, from which no appeal has been or can be taken), the NDA holder is required to promptly notify FDA to withdraw the patent or patent information and request that the patent or patent information be removed from the list. If the NDA holder is required by court order to amend patent information or withdraw a patent from the list, it must submit a copy of the order, within 14 days of the date the order was entered, to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855. FDA will remove a patent from the list if there is no first applicant eligible for 180-day exclusivity or upon the expiration of the 180-day exclusivity period of a first applicant.

(ii) Patent term restoration. If the term of a listed patent is extended under 35 U.S.C. 156(e), the NDA holder must submit on Form FDA 3542 a correction to the expiration date of the patent. This correction must be submitted within 30 days of receipt of a certificate of

extension as described in 35 U.S.C. 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2).

(iii) Submission of corrections or changes to patent information. Corrections or changes to previously submitted patent information, other than withdrawal of a patent and requests to remove a patent from the list, must be submitted on Form FDA 3542 or 3542a, as appropriate. We will not accept the corrections or changes unless they are submitted on the appropriate forms.

(iv) Submission of patent withdrawals and requests to remove a patent from the list. Withdrawal of a patent and requests to remove a patent from the list must be submitted to the same addresses described in paragraph (d)(4) of this section, except that the withdrawal or request to remove a patent from the list is not required to be submitted on Form FDA 3542 and may be submitted by letter. Withdrawal of a patent and a request to delist a patent must contain the following information:

- (A) The NDA number to which the request applies;
- (B) Each product(s) approved in the NDA to which the request applies; and
- (C) The patent number.

6. Section 314.54 is amended by removing the word “shall” and adding in its place the word “must” in paragraph (a)(1) introductory text and paragraph (a)(1)(i) and by revising the section heading, paragraph (a) introductory text, and paragraphs (a)(1)(iii), (a)(1)(vi), (a)(4), and (b) to read as follows:

§ 314.54 Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) The Federal Food, Drug, and Cosmetic Act does not permit approval of an ANDA for a new indication, nor does it permit approval of other changes in a listed drug if investigations,

other than bioavailability or bioequivalence studies, are essential to the approval of the change.

Any person seeking approval of a drug product that represents a modification of a listed drug

(e.g., a new indication or new dosage form) and for which investigations, other than

bioavailability or bioequivalence studies, are essential to the approval of the changes may, except

as provided in paragraph (b) of this section, submit a 505(b)(2) application. This 505(b)(2)

application need contain only that information needed to support the modification(s) of the listed drug.

(1) * * *

(iii) Identification of each listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved NDA number. The listed drug or drugs identified as relied upon must include any approved drug product that:

(A) Is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted; and

(B) Was approved before the 505(b)(2) application was submitted.

* * * * *

(vi) Any patent certification or statement required under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with respect to any relevant patents that claim the listed drug or drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed drug or drug(s).

* * * * *

(4) The applicant must submit a field copy of the 505(b)(2) application that contains the technical section described in § 314.50(d)(1), a copy of the information required under § 314.50(a) and (c), and certification that the field copy is a true copy of the technical section described in § 314.50(d)(1) contained in the archival and review copies of the 505(b)(2) application.

(b) A 505(b)(2) application may not be submitted under this section for a drug product whose only difference from a listed drug is that:

(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the listed drug; or

(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the listed drug.

7. Section 314.60 is amended by:

- a. Removing the word “application” each time it appears and adding in its place “NDA”;
- b. Removing “(505)(c)(3)(D)(ii)” in paragraphs (c)(1)(i) and (c)(2) and adding in its place “(505)(c)(3)(E)(ii)”;
- c. Adding paragraph headings in paragraphs (a), (b), and (c);
- d. Revising the section heading and paragraph (d); and
- e. Adding new paragraphs (e) and (f).

The revisions read as follows:

§ 314.60 Amendments to an unapproved NDA, supplement, or resubmission.

- (a) Submission of NDA. * * *
- (b) Submission of major amendment. * * *
- (c) Limitation on certain amendments. * * *

(d) Field copy. The applicant must submit a field copy of each amendment to a section of the NDA described in § 314.50(d)(1). The applicant must include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(e) Different drug. An applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of this section, a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph, an applicant may amend the 505(b)(2) application to seek approval of a different strength.

(f) Patent certification requirements. An amendment to a 505(b)(2) application is required to contain patent certifications described in § 314.50(i) if approval is sought for any of the following types of amendments:

- (1) To add a new indication or other condition of use;
- (2) To add a new strength;
- (3) To make other than minor changes in product formulation; or
- (4) To change the physical form or crystalline structure of the active ingredient.

8. Section 314.70 is amended by:

- a. Removing the word "application" each time it appears and adding in its place "NDA";
- b. Removing the words "cover letter" in paragraph (a)(6), and adding in their place the word "submission";

- c. Removing the words “and its mailing cover” in paragraph (b)(4);
- d. Revising the section heading and paragraph (f); and
- e. Adding paragraphs (h) and (i).

The revisions read as follows:

§ 314.70 Supplements and other changes to an approved NDA.

* * * * *

(f) Patent information. The applicant must comply with the patent information requirements under section 505(c)(2) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

* * * * *

(h) Different drug. An applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application. For purposes of this section, a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph, an applicant may supplement the 505(b)(2) application to seek approval of a different strength.

(i) Patent certification requirements. (1) Except as provided in paragraph (i)(2) of this section, a supplement to a 505(b)(2) application is required to contain patent certifications described in § 314.50(i) if approval is sought for either of the following types of supplements:

- (i) To add a new indication or other condition of use; or
- (ii) To add a new strength.

(2) A supplement to a 505(b)(2) application that only seeks approval to add a new indication or other condition of use is required to contain patent certifications described in § 314.50(i) only for patents that are identified as claiming an approved use. If a method-of-use patent is identified as also claiming the drug substance or drug product, the patent certification also must address the drug substance and/or drug product claims.

9. Section 314.90 is amended by removing the word “application” each time it appears and adding in its place “NDA” and by adding paragraph (c) to read as follows:

§ 314.90 Waivers.

* * * * *

(c) If FDA grants the applicant’s waiver request with respect to a requirement under §§ 314.50 through 314.81, the waived requirement will not constitute a basis for refusal to approve an NDA under § 314.125.

10. Section 314.93 is amended by:

- a. Removing the words “abbreviated new drug applications” in paragraph (a) and adding in their place “ANDAs”;
- b. Removing the words “abbreviated new drug application” in paragraphs (b), (c), and (e)(3) and adding in their place “ANDA”;
- c. Removing the word “or” from the end of paragraph (e)(1)(iv) ;
- d. Removing “reasons.” in paragraph (e)(1)(v) and adding in its place “reasons; or”;
- e. Adding paragraph (e)(1)(vi);
- f. Redesignating paragraph (f) as paragraph (f)(1); and
- g. Adding paragraph (f)(2).

The revisions read as follows:

§ 314.93 Petition to request a change from a listed drug.

* * * *

(e) * * *

(1) * * *

(vi) A drug product is approved in an NDA for the change described in the petition.

* * * *

(f) * * *

(2) If, after approval of a petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the petition and the listed drug identified in the petition can no longer be the basis for ANDA submission, irrespective of whether FDA has withdrawn approval of the petition. A person seeking approval for such drug product must submit a new ANDA that identifies the pharmaceutically equivalent reference listed drug as the basis for ANDA submission and comply with applicable regulatory requirements.

11. Section 314.94 is amended by:

- a. Removing the words “abbreviated application” in paragraphs (a)(5)(ii)(A), (a)(6)(ii), (d)(1)(i), and (d)(4) each time they appear and adding in their place “ANDA”;
- b. Removing the word “shall” in paragraphs (a)(9)(i) through (a)(9)(iv), (a)(12)(i)(A)(1) through (a)(12)(i)(A)(3), and (a)(12)(vii) each time it appears and adding in its place the word “must”;
- c. Removing and reserving paragraph (a)(12)(iv); and
- d. Revising the section heading and the introductory text, paragraph (a) heading and introductory text, paragraphs (a)(1) and (a)(2), paragraph (a)(3) heading and introductory text,

paragraphs (a)(3)(i), (a)(3)(iii), the first sentence of paragraph (a)(7)(ii), paragraphs (a)(7)(iii), (a)(8)(i), (a)(9)(v), paragraph (a)(12)(i)(A) introductory text, paragraphs (a)(12)(i)(A)(4), (a)(12)(i)(B), (a)(12)(iii)(A), (a)(12)(iii)(B), (a)(12)(v), (a)(12)(vi), (a)(12)(viii), (a)(13), (b), paragraph (d) heading, paragraph (d)(1) introductory text, and paragraphs (d)(2) and (d)(5).

The revisions read as follows:

§ 314.94 Content and format of an ANDA.

ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the application are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

(a) ANDAs. Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the ANDA that includes the following:

(1) Application form. The applicant must submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant must state whether the submission is an ANDA under this section or a supplement to an ANDA under § 314.97.

(2) Table of contents. The archival copy of the ANDA is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) Basis for ANDA submission. An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the Agency as the reference standard for conducting bioequivalence testing. The application must contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an ANDA based on an approved petition under § 10.30 of this chapter or § 314.93, the reference listed drug must be the same as the listed drug approved in the petition.

* * * * *

(iii) For an ANDA based on an approved petition under § 10.30 of this chapter or § 314.93, a reference to the FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

* * * * *

(7) * * *

(ii) If the ANDA is submitted pursuant to a petition approved under § 314.93, the results of any bioavailability or bioequivalence testing required by the Agency, or any other information required by the Agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. * * *

* * * * *

(iii) For each in vivo or in vitro bioequivalence study contained in the ANDA:

(A) A description of the analytical and statistical methods used in each study; and

(B) With respect to each study involving human subjects, a statement that it either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) Labeling--(i) Listed drug labeling. A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the ANDA, if the ANDA relies on a reference listed drug.

* * * *

(9) * * *

(v) Inactive ingredient changes permitted in drug products intended for topical use. Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions must contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

* * * *

(12) Patent certification--(i) Patents claiming drug, drug product, or method of use. (A) A certification with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

* * * *

(4) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. The applicant shall entitle such a certification “Paragraph IV Certification”. This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. _____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, with the requirements under § 314.95(b) with respect to sending the notice, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the ANDA refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, the appropriate patent certification under paragraph (a)(12)(i) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

* * * * *

(iii) Method-of-use patent. (A) If patent information is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications or other conditions of use that are covered by the use patent, a statement explaining that the method-of-use patent does not claim any of the proposed indications or other conditions of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) [Reserved]

(v) Licensing agreements. If the ANDA is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, a paragraph IV certification as to that patent and a statement that it has been granted a patent license.

(vi) Untimely filing of patent information. If a patent on the listed drug is issued and the holder of the approved NDA for the listed drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an ANDA for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification to address the patent that is late-listed with respect to the pending ANDA. Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if:

(A) The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or

(B) The amendment is submitted more than 30 days after a corresponding change in approved product labeling. An applicant whose ANDA is submitted after the NDA holder's untimely filing of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, must submit a

certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.

* * * * *

(viii) Amended certifications. A certification submitted under paragraphs (a)(12)(i) through (a)(12)(iii) of this section may be amended at any time before the date of approval of the ANDA. If an applicant with a pending ANDA voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant must submit an amended certification as an amendment to a pending ANDA. Once an amendment is submitted to change a certification, the ANDA will no longer be considered to contain the prior certification.

(A) After finding of infringement. An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date. Once an amendment for the change has been submitted, the ANDA will no longer be considered to be one containing a paragraph IV certification to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) After request to remove a patent or patent information from the list. If the list reflects that an NDA holder has requested that a patent be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent

will be removed and any applicant with a pending ANDA (including a tentatively approved application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification (that the patent is or has been removed from the list). If the list reflects that an NDA holder has requested that a patent be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent shall remain listed until any 180-day exclusivity is extinguished. If one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to a patent that has been reissued, then the first applicant must submit a paragraph IV certification to the reissued patent within 30 days of listing to have lawfully maintained its paragraph IV certification for purposes of eligibility for 180-day exclusivity. After any applicable 180-day exclusivity has been extinguished, the patent will be removed and any applicant with a pending ANDA (including a tentatively approved application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. Once an amendment to withdraw the certification has been submitted, the ANDA will no longer be considered to be one containing a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are no listed patents.

(C) Other amendments. (1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(2) of this section:

(i) An applicant must amend a submitted certification if, at any time before the date of approval of the ANDA, the applicant learns that the submitted certification is no longer accurate; and

(ii) An applicant must submit a certification or statement under paragraph (a)(12)(i) of this section if, after submission of the ANDA, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims an approved use for such reference listed drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

(2) An applicant is not required to submit a supplement to change a submitted certification when information on a patent on the listed drug is submitted after the approval of the ANDA, except as provided in § 314.97(c).

(13) Financial certification or disclosure statement. An ANDA must contain a financial certification or disclosure statement as required by part 54 of this chapter.

(b) Drug products subject to the Drug Efficacy Study Implementation (DESI) review. If the ANDA is for a duplicate of a drug product that is subject to FDA's DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant must comply with the provisions of paragraph (a) of this section.

(c) [Reserved]

(d) Format of an ANDA. (1) The applicant must submit a complete archival copy of the ANDA as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the ANDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ANDA, to give other Agency

personnel access to the ANDA for official business, and to maintain in one place a complete copy of the ANDA.

* * * * *

(2) For ANDAs, the applicant must submit a review copy of the ANDA that contains two separate sections. One section must contain the information described under paragraphs (a)(2) through (a)(6), (a)(8), and (a)(9) of this section, and section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and a copy of the analytical procedures and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical procedures. The other section must contain the information described under paragraphs (a)(3), (a)(7), and (a)(8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under § 314.50(a).

* * * * *

(5) The applicant must submit a field copy of the ANDA that contains the technical section described in paragraph (a)(9) of this section, a copy of the application form required under paragraph (a)(1) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (a)(9) of this section contained in the archival and review copies of the ANDA.

12. Section 314.95 is revised to read as follows:

§ 314.95 Notice of certification of invalidity or noninfringement of a patent.

(a) Notice of certification. For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and for which the applicant submits a paragraph IV certification, the applicant must send notice of such certification by

registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section to each of the following persons:

(1) Each owner of the patent which is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the listed drug that is claimed by the patent and for which the applicant is seeking approval or, if the NDA holder does not reside or maintain a place of business within the United States, the NDA holder's attorney, agent, or other authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained from the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855.

(3) This paragraph does not apply to a use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) Sending the notice. (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date it receives an acknowledgment letter or a paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark on the acknowledgment letter. The 20-day clock described in this paragraph begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the applicant's receipt of an acknowledgment letter or a paragraph IV acknowledgment letter, or before the first working day after the day the patent is published in the list. The applicant will not have complied with this paragraph until it sends valid notice.

(3) At the same time it sends the notice required by paragraph (a) of this section, the applicant must submit to FDA an amendment to its ANDA that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirements under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) Contents of a notice. In the notice, the applicant must cite section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and must include, but is not limited to, the following information:

(1) A statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The ANDA number.

(3) A statement that the applicant has received the acknowledgment letter or paragraph IV acknowledgment letter for the ANDA.

(4) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(5) The active ingredient, strength, and dosage form of the proposed drug product.

(6) The patent number and expiration date of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.

(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(8) If the applicant alleges that the patent will not be infringed and the applicant may later decide to file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) Amendment or supplement to an ANDA. (1) If, after receipt of a paragraph IV acknowledgment letter, an applicant submits an amendment or supplement to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the ANDA is submitted to FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(2) If, before receipt of an acknowledgment letter or a paragraph IV acknowledgment letter, an applicant submits an amendment to its ANDA that includes a paragraph IV

certification, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section. If an ANDA applicant's notice of its paragraph IV certification is timely provided in accordance with paragraph (b) of this section, FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (d)(2) of this section, as applicable.

(e) Documentation of timely sending and receipt of notice. The applicant must amend its ANDA to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or paragraph (d) of this section, as applicable, and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) that includes the patent that is the subject of the paragraph IV certification. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person who provided the notice. An applicant may rely on another

form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) Approval. If the requirements of this section are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder as the first day of the 45-day period provided for in section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant provides a written statement to FDA that a later date should be used, count from such later date.

(g) Designated delivery services. (1) For purposes of this section, the term “designated delivery service” means any delivery service provided by a trade or business that the Agency determines:

- (i) Is available to the general public throughout the United States;
- (ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and
- (iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA will periodically issue guidance regarding designated delivery services that meet these criteria.

13. Section 314.96 is amended by:

- a. Revising the section heading;
- b. Removing from the heading of paragraph (a) and from paragraph (a)(1) the words “abbreviated new drug application” and adding in their place “ANDA”;
- c. Removing from paragraph (a)(1) “320.1(g)” and adding in its place “314.3”;

d. Removing from paragraph (b) the word “shall” each time it appears and adding in its place the word “must”;

e. Adding a heading to paragraph (b); and

f. Adding paragraphs (c) and (d).

The revisions read as follows:

§ 314.96 Amendments to an unapproved ANDA.

* * * * *

(b) Field copy. * * *

(c) Different listed drug. An applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the reference listed drug identified in the ANDA. This paragraph applies if, at any time before the approval of the ANDA, a different listed drug is approved that is the pharmaceutical equivalent to the product in the ANDA and is designated as a reference listed drug. This paragraph also applies if changes are proposed in an amendment to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of the reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph, an applicant may amend the ANDA to seek approval of a different strength.

(d) Patent certification requirements. An amendment to an ANDA is required to contain patent certifications described in § 314.94(a)(12) if approval is sought for any of the following types of amendments:

(1) To add a new indication or other condition of use;

(2) To add a new strength;

- (3) To make other than minor changes in product formulation; or
- (4) To change the physical form or crystalline structure of the active ingredient.

14. Section 314.97 is revised to read as follows:

§ 314.97 Supplements and other changes to an approved ANDA.

(a) General requirements. The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved ANDA.

(b) Different listed drug. An applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current reference listed drug identified in the ANDA. This paragraph applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph, an applicant may supplement the ANDA to seek approval of a different strength.

(c) Patent certification requirements. A supplement to an ANDA is required to contain patent certifications described in § 314.94(a)(12) if approval is sought for either of the following types of supplements:

- (1) To add a new indication or other condition of use; or
- (2) To add a new strength.

15. Section 314.99 is revised to read as follows:

§ 314.99 Other responsibilities of an applicant of an ANDA.

(a) An applicant must comply with the requirements of § 314.65 regarding withdrawal by the applicant of an unapproved ANDA and § 314.72 regarding a change in ownership of an ANDA.

(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant must comply with the requirements for a waiver under § 314.90. If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.

16. Section 314.101 is revised to read as follows:

§ 314.101 Filing an NDA and receiving an ANDA.

(a) Filing an NDA. (1) Within 60 days after FDA receives an NDA, the Agency will determine whether the NDA may be filed. The filing of an NDA means that FDA has made a threshold determination that the NDA is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the NDA applies, the Agency will file the NDA and notify the applicant in writing. In the case of a 505(b)(2) application that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter. The date of filing will be the date 60 days after the date FDA received the NDA. The date of filing begins the 180-day period described in section 505(c) of the Federal Food, Drug, and Cosmetic Act. This 180-day period is called the "filing clock."

(3) If FDA refuses to file the NDA, the Agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file

the NDA under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the Agency's notification an informal conference with the Agency about whether the Agency should file the NDA. If, following the informal conference, the applicant requests that FDA file the NDA (with or without amendments to correct the deficiencies), the Agency will file the NDA over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the NDA is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an NDA that is filed over protest. If FDA refuses to file the NDA under paragraph (e) of this section, the applicant may amend the NDA and resubmit it, and the Agency will make a determination under this section whether it may be filed.

(b) Receiving an ANDA. (1) An ANDA will be reviewed after it is submitted to determine whether the ANDA may be received. Receipt of an ANDA means that FDA has made a threshold determination that the ANDA is substantially complete.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the ANDA not to have been received applies, the ANDA is substantially complete and the Agency will receive the ANDA and notify the applicant in writing. If an ANDA is determined to be substantially complete, the date of submission is considered to be the date of receipt. In the case of an ANDA that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter.

(3) If FDA considers the ANDA not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant. The applicant may then:

- (i) Withdraw the ANDA under § 314.99; or
- (ii) Amend the ANDA to correct the deficiencies; or

(iii) Take no action, in which case FDA will refuse to receive the ANDA.

(4) If, after an ANDA has been received under paragraph (b)(2) of this section, FDA determines that the applicant did not send notice of a paragraph IV certification as required under § 314.95 within the timeframe specified in paragraph (b) or (d) of that section, the date that the ANDA was submitted will be deemed to be delayed by the number of days by which the timeframe required by § 314.95(b) or (d) was exceeded. When the date as delayed falls on Saturday, Sunday, or a Federal holiday, the filing date will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(c) [Reserved]

(d) Application deficiencies. FDA may refuse to file an NDA or may not consider an ANDA to be received if any of the following applies:

(1) The NDA or ANDA does not contain a completed application form.

(2) The NDA or ANDA is not submitted in the form required under § 314.50 or § 314.94.

(3) The NDA or ANDA is incomplete because it does not on its face contain information required under section 505(b) or section 505(j) of the Federal Food, Drug, and Cosmetic Act and § 314.50 or § 314.94.

(4) The applicant fails to submit a complete environmental assessment that addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(5) The NDA or ANDA does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The NDA or ANDA does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in part 58 of this chapter or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The NDA or ANDA does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter or, if the study was subject to but was not conducted in compliance with those regulations, the NDA or ANDA does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved NDA or ANDA and the applicant of the submission:

- (i) Has an approved NDA or ANDA for the same drug product; or
- (ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

(e) Regulatory deficiencies. The Agency will refuse to file an NDA or will consider an ANDA not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 et seq.) and subchapter F of this chapter.

(2) Submission of a 505(b)(2) application or an ANDA for the active moiety is not permitted under § 314.108(b)(2).

(f) Outcome of FDA review. (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the NDA; or

(ii) Issue a notice of opportunity for a hearing if the applicant asked FDA to provide it an opportunity for a hearing on an NDA in response to a complete response letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the ANDA. If FDA disapproves the ANDA, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an ANDA in response to a complete response letter.

(3) This paragraph does not apply to NDAs or ANDAs that have been withdrawn from FDA review by the applicant.

17. Section 314.105 is revised to read as follows:

§ 314.105 Approval of an NDA and an ANDA.

(a) FDA will approve an NDA and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the NDA applies. An NDA is approved on the date of the issuance of the approval letter. FDA will issue a tentative approval letter if an NDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31, or if a 505(b)(2) application otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(3) or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; or because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug,

and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the NDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of the approval letter.

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling, and an ANDA after it determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy.

(d) FDA will approve an ANDA and send the applicant an approval letter if none of the reasons in § 314.127 for refusing to approve the ANDA applies. The date of approval is the date of the issuance of the Agency's approval letter. FDA will issue a tentative approval letter if an ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31, or cannot be approved until the conditions in § 314.107(b)(3) or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; or because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the ANDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of the approval letter.

18. Section 314.107 is revised to read as follows:

§ 314.107 Date of approval of a 505(b)(2) application or ANDA.

(a) General. A drug product may be introduced or delivered for introduction into interstate commerce when the 505(b)(2) application or ANDA for the drug product is approved. A 505(b)(2) application or ANDA for a drug product is approved on the date FDA issues an approval letter under § 314.105 for the 505(b)(2) application or ANDA.

(b) Effect of patent(s) on the listed drug. As described in paragraphs (b)(1) and (b)(2) of this section, the status of patents listed for the listed drug(s) relied upon or reference listed drug, as applicable, must be considered in determining the first possible date of approval of a 505(b)(2) application or ANDA. The criteria in paragraphs (b)(1) and (b)(2) of this section will be used to determine, for each relevant patent, the date that patent will no longer prevent approval. The first possible date of approval will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.

(1) Timing of approval based on patent certification or statement. If none of the reasons in § 314.125 or § 314.127 for refusing to approve the application applies, and none of the reasons in paragraph (d) of this section for delaying approval applies, the 505(b)(2) application or ANDA may be approved as follows:

(i) Immediately, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(A) The applicant is aware of a relevant patent but the patent information required under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act has not been submitted to FDA; or

(B) The relevant patent has expired; or

(C) The relevant patent is invalid, unenforceable, or will not be infringed, except as provided in paragraphs (b)(3) and (c) of this section, and the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act has expired; or

(D) There are no relevant patents.

(ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval.

(iii) On the date specified, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date.

(2) Patent information filed after submission of 505(b)(2) application or ANDA. If the holder of the approved NDA for the listed drug submits patent information required under § 314.53 after the date on which the 505(b)(2) application or ANDA was submitted to FDA, the 505(b)(2) applicant or ANDA applicant must comply with the requirements of § 314.50(i)(4) and (i)(6) and § 314.94(a)(12)(vi) and (a)(12)(viii) regarding amendment of its patent certification or statement. If the applicant submits an amendment certifying under § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4) that the relevant patent is invalid, unenforceable, or will not be infringed, and complies with the requirements of § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification under § 314.52(e) or § 314.95(e). The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act does not apply in these circumstances.

(3) Disposition of patent litigation--(i) Approval upon expiration of 30-month period or 7½ years from date of reference product approval. (A) Except as provided in paragraphs (b)(3)(ii) through (b)(3)(viii) of this section, if, with respect to patents for which required information was submitted under § 314.53 before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA), the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the

relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved 30 months after the later of the date of the receipt of the notice of certification by any owner of the listed patent or by the NDA holder who is an exclusive patent licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved at the expiration of 7½ years from the date of approval of the NDA for the patented drug product.

(ii) Federal district court decision of invalidity, unenforceability, or non-infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the court enters judgment reflecting the decision; or

(B) The date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed.

(iii) Appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is appealed, the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(B) The date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed.

(iv) Affirmation or non-appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A).

(v) Grant of preliminary injunction by Federal district court. If before the expiration of the 30-month period, or 7½ years where applicable, the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(ii) of this section. If the court decides that the patent has been infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (b)(3)(iv) of this section, whichever is applicable.

(vi) Written consent to approval by patent owner or exclusive patent licensee. If before the expiration of the 30-month period, or 7½ years where applicable, the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

(vii) Court order terminating 30-month or 7½ year period. If before the expiration of the 30-month period, or 7½ years where applicable, the court enters an order requiring the 30-month or 7½-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order.

(viii) Court order of dismissal without a finding of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the court enters an order of dismissal, with or without prejudice, without a finding of infringement, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

(4) Tentative approval. FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with paragraphs (b)(3) or (e)(1)(vi) of this section. In order for a 505(b)(2) application or ANDA to be approved under paragraph (b)(3) of this section, the applicant must receive an approval letter from the Agency. Tentative approval of an application does not constitute “approval” of an application and cannot, absent an approval letter from the Agency, result in an approval under paragraph (b)(3) of this section.

(c) Subsequent ANDA submission. (1) If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as the ANDA of a subsequent applicant. The ANDA of a subsequent applicant will not be approved during the period when any first applicant is eligible for 180-day exclusivity or during the 180-

day exclusivity period of a first applicant. Any applicable 180-day exclusivity period cannot extend beyond the expiration of the patent upon which the 180-day exclusivity period was based.

(2) For purposes of paragraph (c)(1) of this section, a first applicant must submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of its drug product. If an applicant does not notify FDA, as required in this paragraph, of this date, the date of first commercial marketing will be deemed to be the date of the drug product's approval.

(d) Delay due to exclusivity. The Agency will also delay the approval of a 505(b)(2) application or an ANDA if delay is required by the exclusivity provisions in § 314.108, § 316.31, or section 505A of the Federal Food, Drug, and Cosmetic Act. When the approval of a 505(b)(2) application or ANDA is delayed under this section and § 314.108, § 316.31, or section 505A of the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application or ANDA will be approved on the latest of the days specified under this section and § 314.108, § 316.31, or section 505A of the Federal Food, Drug, and Cosmetic Act, as applicable.

(e) Notification of court actions or documented agreement. (1) The applicant must submit the following information to FDA, as applicable:

(i) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in paragraph (b)(3) of this section invalid, unenforceable, or not infringed, or finding the patent valid and infringed;

(ii) Written notification of whether or not any action by the court described in paragraph (e)(1)(i) of this section has been appealed within the time permitted for an appeal;

(iii) A copy of any order entered by the court terminating the 30-month or 7½-year period described in paragraphs (b)(3)(i) and (b)(3)(ii) of this section;

(iv) A copy of any documented agreement described in paragraph (b)(3)(vi) of this section;

(v) A copy of any preliminary injunction described in paragraph (b)(3)(v) of this section, and a copy of any subsequent court order lifting the injunction; and

(vi) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in paragraph (b)(3) of this section).

(2) All information required by paragraph (e)(1) of this section must be sent to the Office of Generic Drugs (HFD-600) or to the appropriate division in the Office of New Drugs within 14 days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of documented agreement, as applicable.

(f) Forty-five day period after receipt of notice of paragraph IV certification--(1)
Computation of 45-day time clock. The 45-day clock described in paragraph (b)(3) of this section as to each recipient required to receive notice of paragraph IV certification under § 314.52 or § 314.95 begins on the day after the date of receipt of the applicant's notice of paragraph IV certification by the recipient. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) Notification of filing of legal action. (i) The 505(b)(2) or ANDA applicant must notify FDA in writing within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. A 505(b)(2) applicant must

send the notification to the appropriate division in the Office of New Drugs reviewing the 505(b)(2) application. An ANDA applicant must send the notification to FDA's Office of Generic Drugs (HFD-600). The notification to FDA of the legal action must include:

(A) The 505(b)(2) application or ANDA number.

(B) The name of the 505(b)(2) or ANDA applicant.

(C) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(D) A statement that an action for patent infringement, identified by the court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

(ii) A patent owner or NDA holder (or their representatives) may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in paragraph (f)(2)(i) of this section.

(iii) If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or their representatives do not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of the Agency's review of the 505(b)(2) application or ANDA, whichever is later.

(3) Waiver. If the patent owner or NDA holder who is an exclusive patent licensee (or their representatives) waives its opportunity to file a legal action for patent infringement within

45 days of a receipt of the notice of certification and the patent owner or NDA holder who is an exclusive patent licensee (or their representatives) submits to FDA a valid waiver before the 45 days elapse, the 505(b)(2) application or ANDA may be approved upon completion of the Agency's review of the application. FDA will only accept a waiver in the following form:

(Name of patent owner or NDA holder who is an exclusive patent licensee or their representatives) has received notice from (name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act) and does not intend to file an action for patent infringement against (name of applicant) concerning the drug (name of drug) before (date on which 45 days elapses). (Name of patent owner or NDA holder who is an exclusive patent licensee) waives the opportunity provided by (section 505(c)(3)(C) or 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act) and does not object to FDA's approval of (name of applicant)'s (505(b)(2) application or ANDA) for (name of drug) with an approval date on or after the date of this submission.

(g) Conversion of approval to tentative approval. If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.

19. Section 314.108 is amended by:

- a. Revising paragraph (a) introductory text and the definitions of "Approved under section 505(b)", "Essential to approval", and "New chemical entity";
- b. Removing from paragraph (a) the definitions of "Active moiety", "Date of approval", and "FDA";
- c. Adding alphabetically to paragraph (a) the definition of "Bioavailability study"; and
- d. Revising paragraph (b).

The revisions read as follows:

§ 314.108 New drug product exclusivity.

(a) Definitions. The definitions at § 314.3 and the following definitions of terms apply to this section:

Approved under section 505(b) means an NDA submitted under section 505(b) and approved on or after October 10, 1962, or an application that was “deemed approved” under section 107(c)(2) of Public Law 87-781.

Bioavailability study means a study to determine the bioavailability or the pharmacokinetics of a drug.

* * * * *

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the NDA.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

* * * * *

(b) Submission of and date of approval of a 505(b)(2) application or ANDA.

(1) [Reserved]

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, no person may submit a 505(b)(2) application or ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved NDA, except that the 505(b)(2) application or ANDA may be submitted after 4 years if it contains a

certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

(3) The approval of a 505(b)(2) application or ANDA described in paragraph (b)(2) of this section will occur as provided in § 314.107(b)(1) or (b)(2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the NDA for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or ANDA will occur as provided in § 314.107(b)(3).

(4) If an NDA:

(i) Was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, for a period of 3 years after the date of approval of the application, the Agency will not approve a 505(b)(2) application or an ANDA for the conditions of approval of the original NDA, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting the conditions of approval of an original NDA.

(5) If a supplemental NDA:

(i) Was approved after September 24, 1984; and

(ii) Contained reports of new clinical investigations (other than bioavailability studies)

that were conducted or sponsored by the applicant that were essential to approval of the supplemental NDA, for a period of 3 years after the date of approval of the supplemental application, the Agency will not approve a 505(b)(2) application or an ANDA for a change, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting a change approved in the supplemental NDA.

20. Section 314.125 is amended by:

a. Removing the word “application” wherever it appears in the section heading, paragraph (a) introductory text, and paragraphs (a)(2), (b)(7), (b)(9), (b)(10), (b)(12), and (b)(14) through (b)(18) and adding in its place “NDA”;

b. Revising paragraph (b) introductory text; and

c. Adding paragraph (b)(19).

The revisions read as follows:

§ 314.125 Refusal to approve an NDA.

* * * * *

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

* * * * *

(19) The 505(b)(2) application failed to contain a patent certification or statement with respect to each listed patent for an approved drug product that:

(i) Is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted; and

(ii) Was approved before the 505(b)(2) application was submitted.

* * * * *

21. Section 314.127 is amended by:

a. Removing the words “abbreviated application” and “abbreviated new drug application” wherever they appear in paragraphs (a) and (b) and adding in their place “ANDA”;

b. Revising the section heading and paragraph (a) introductory text; and

c. Adding paragraph (a)(14).

The revisions read as follows:

§ 314.127 Refusal to approve an ANDA.

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

* * * * *

(14) For an ANDA submitted pursuant to an approved suitability petition, an NDA subsequently has been approved for the change described in the suitability petition.

* * * * *

PART 320--BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

22. The authority citation for part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

23. Section 320.1 is revised to read as follows:

§ 320.1 Definitions.

The definitions contained in § 314.3 of this chapter apply to those terms when used in this part.

24. Section 320.23 is amended by:

- a. Revising the last sentence in paragraph (a)(1);
- b. Removing the word “shall” in paragraph (a)(2) and adding in its place the word “must”;
- c. Redesignating paragraph (b) as paragraph (b)(1); and
- d. Adding new paragraph (b)(2).

The revisions read as follows:

§ 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.

(a)(1) * * * For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

* * * * *

(b) * * *

(2) For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

Dated: January 23, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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